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Progress Report No. 13

Biomedical Computer Laboratory

PROGRESS REPORT

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Biomedical Computer Laboratory

Washington University School of Medicine

700 South Euclid Ave.

St. Louis, Missouri 63110

BIOMEDICAL COMPUTER LABORATORY

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

PROGRESS REPORT NO. 13

JULY 1, 1976 - JUNE 30, 1977

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I. INTRODUCTION

This progress report from the Biomedical Computer Laboratory (BCL) summarizes work done during the period from July 1, 1976 through June 30, 1977. The Biomedical Computer Laboratory collaborates with research investigators throughout the Washington University School of Medicine and its affiliated hospitals in the application of advanced computer techniques to problems in biology and medicine. This often requires work in areas stretching from basic physiology through mathematical models to equipment design. Our orientation is interdisciplinary with the recognition that effective communication for workers with differing backgrounds comes only through extended collaboration and mutual respect.

The vigorous development and evolution of specialized computer systems for use in the solution of research and clinical problems has continued to be the central focus of BCL activities. Several systems now in clinical use have seen a progression from exploratory pilot studies, to major developmental project, to local clinical trial, to clinical trials in multiple locations, to public availability through commercial manufacture. Perseverance in this sometimes tedious chain of development has found reward in the effective fielding of specialized computer systems to the medical community.

One class of computer applications requires strong coupling of the computer to its environment for digital signal processing. These applications typically involve the use of commercially available minicomputers and microprocessors in conjunction with specialized hardware designed and built locally. We have pursued many such applications by bringing signals from hospital wards and research laboratories to BCL by means of either analog or digital tape recordings or telephone lines and, more frequently, by taking the computers to the investigator's laboratory or the patient's bedside.

For those classes of applications dominated by information processing requirements, provisions have matured from telephone lines linking our minicomputers to the IBM System/360, Model 65 at the Washington University Computing Facilities, through development and support of a minicomputer based MUMPS system, to the establishment of an independent Medical Computing Facility to serve the local medical complex. Diverse needs continue to be met by these various options while collaborative work continues on more advanced information-processing developments.

Still another class of applications requires extensive use of large-scale computational services. Many investigators are assisted in their research through the use of generalized numerical, non-numerical, and statistical routines. This work is carried out in part by staff members of BCL, but primarily by members of the Division of Biostatistics under the direction of Dr. Reimut Wette, and the University Computing Facilities whose director is Robert J. Benson.

The BCL enjoys collaborations with over 15 departmental divisions within the medical school but also finds support and enrichment through close ties with other facilities throughout the University. These arrangements are of benefit both to the BCL and to graduate students who find projects and employment among the activities in the laboratory. The Department of Computer Science is under the direction of Dr. Jerome R. Cox, Jr., past Director of the BCL. Close collaboration with that department currently emphasizes the area of information systems. Strong ties with the Department of Electrical Engineering are sustained through its Biomedical Engineering Program and common interests in digital signal processing techniques. The Department of Electrical Engineering is chaired by Dr. Donald L. Snyder, past Associate Director of BCL.

The Washington University Computer Laboratories (WUCL) is a federation of computer research activities which includes the Biomedical Computer Laboratory and the Computer Systems Laboratory. This federation of laboratories functions through a coordinating committee composed of the laboratory directors and in addition, the Vice Chancellor for Medical Affairs, the Associate Vice Chancellor for Research, the Director of the University Computing Facilities and the Associate Directors of both laboratories.

The Computer Systems Laboratory, which is under the direction of Dr. Charles E. Molnar, is active in the design, development, evaluation and application of a compatible set of "macromodules" useful in the experimental design of arbitrarily large, complex, asynchronous, specialized computer systems. An important current project is aimed at producing and supporting a high-performance replicable graphics and modeling system that can be acquired by research groups elsewhere.

A National Advisory Panel assists in planning health-related activities of the Biomedical Computer Laboratory and Computer Systems Laboratory under a grant from the Biotechnology Resources Program, Division of Research Resources, National Institutes of Health. Currently the Committee has the following membership:

W. A. Clark	Consultant and Past Director of Computer Systems Laboratory	Cambridge, Massachusetts
D. M. Kipnis	Busch Professor and Head of the Department of Medicine	Washington University School of Medicine
F. M. Richards	Professor in Molecular Biophysics and Chemistry	Yale University
R. S. Snider	Professor of Anatomy and Director of Center for Brain Research	University of Rochester

The Advisory Committee meets periodically with the WUCL Coordinating Committee to review developing projects and programs and to advise on desirable areas of applications.

II. SOURCES OF SUPPORT

During the period covered by this report the primary source of support for the Biomedical Computer Laboratory was a grant from the National Institutes of Health:

RR 00396	A Resource for Biomedical Computing

A research grant to study the relationship of arrhythmias and sudden death sponsored by the National Heart, Lung and Blood Institute has continued in collaboration with the Department of Medicine and the Jewish Hospital:

HL 18808	Prediction and Prevention of Sudden Cardiac Death

A research grant was awarded to support activities of information exchange about MUMPS and MUMPS application transfers:

HS 01540	Pilot Project, MUMPS Users' Group

A subcontract was awarded to establish a data management system for the research supported by NHLBI contract NO1 HZ 62960 awarded to St. Louis University.

Another subcontract was awarded with The Jewish Hospital of St. Louis for research sponsored by their contract with Sandoz-Wander, Inc.

Funds were received under a Special Projects Grant from the State of Missouri to establish a perinatal database at the St. Louis Children's Hospital.

Collaboration with other investigators often involved work already supported by other grants. Most of this support was from the Public Health Service:

AM 17904	Diabetes and Endocrinology Center
CA 08759	Structure and Biologic Function Glycoproteins
EY 00336	Glaucoma Clinical Research Center
GM 13925	Structural Studies on Dehydrogenases and Lipoproteins
HL 07081	Multi Disciplinary Heart and Vascular Diseases
HL 12820	Lipid Protein Interactions in Blood Clotting
HL 13851	Cyclotron Produced Isotopes in Biology and Medicine
HL 14147	Specialized Center of Research in Thrombosis

HL 17646	Study of Ischemic Heart Disease
HL 18144	Preprocessor System for Cardiograms
HS 00074	Technology and Health Care
NS 03856	Auditory Communication and its Disorders
NS 04513	Coordinated Basic and Clinical Brain Research Program
NS 06833	An Interdisciplinary Stroke Program
NS 06947	Bioelectric Studies of Cerebral Cortex
NS 11059	Brain Studies with Positron-Emitting Radiopharmaceuticals
RR 00954	A Resource for Biomedical Mass Spectrometry

III. PERSONNEL

EMPLOYEES

Personnel employed by the Biomedical Computer Laboratory during the period covered by this report were:

Director

Lewis J. Thomas, Jr., M.D.

Assistant Directors

G. James Blaine, III, D.Sc.
V. W. Gerth, Jr., M.S.

Business Manager

Virginia M. Bixon, B.S.

Senior Research Associate

Jerome R. Cox, Jr., Sc.D., and Chairman and Professor of Computer Science

Research Associates

Robert J. Arnzen, Ph.D., and Computer Systems Laboratory
R. Martin Arthur, Ph.D., and Associate Professor of Electrical Engineering
A. Maynard Engebretson, D.Sc., and Central Institute for the Deaf
Philip M. Fishman, D.Sc., and Research Instructor in Computer Science in Psychiatry
William F. Holmes, Ph.D., and Associate Professor of Biological Chemistry
Kenneth B. Larson, Ph.D.
Thomas F. Martin, M.D., and Assistant Professor of Clinical Medicine
Donald L. Snyder, Ph.D., and Chairman and Professor of Electrical Engineering
Joan Zimmerman, D.Phil.

Visiting Scientist

C. Franklin Starmer, Jr., Ph.D.

Research Assistants

H. Dieter Ambos
Philip S. Berger, M.S.
Andrew L. Bodicky, B.S.
Gary H. Brandenburger, M.S.
Michael W. Browder, M.S.
Kenneth W. Clark, M.S.
Stanley A. Garfield, B.S.

Robert H. Greenfield, D.Sc.
Ronald W. Hagen, M.S.
Ross K. Hartz, B.S.
Barry R. Hieb, M.D.
Richard E. Hitchens, B.S.
Frank Hummel, M.S.
Janet A. Johnson, B.S.
Margaret C. Jost, M.S.
Joanne Markham, M.S.
Charles N. Mead, M.D.
J. Philip Miller, B.A.
Patricia Moore, Ph.D.
Nizar A. Mullani, B.S.
Jeffrey C. Nathanson, B.S.
Michael A. Province, B.A.
Sandra L. Rankin, B.S.
Don L. Rempel, M.S.
Michael C. Rigden, A.B.
Kenneth L. Ripley, M.S.
J. Alan Ritter, S.B.
Bruce F. Spenner, D.Sc.
Robert K. Stimac, B.S.
David K. Tao, D.Sc.
David M. Ungar, M.S.
Nageswara R. Vemula, M.S.
M. Jane Wright, B.S.
Budimir Zvolanek, B.S.

Engineering Assistants

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Wayne R. Roloff, B.S.
Marc L. Smith, M.S.

Technical Assistants

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Gerald A. Burger, B.S.
Alice A. Camuto, A.B.
Gary R. Cook, B.A.
David C. Ficke, B.S.
Geraldine C. Hall
Margaret A. Hug
Ronnie S. Malamud
Susan E. Menner
John R. Meuleman
Stephen M. Moore
Stanford M. Moran, B.S.
Lorin D. Peterson, B.S.
Stephen J. Potter
Jeffrey M. Shapiro, B.S.
David L. Shupe

Electronics Technicians

Theron R. Baird
George L. Bickmore
Paul J. Hasser
Thomas J. Marshall, B.S.
Remo Moroni, III
Robert R. Peglar
David T. Taylor

Librarian

Beth E. Robinson, M.L.S.

Secretaries

Shirley A. Gonzalez-Rubio
Betty L. Hill
Clara E. Ingersoll
Sandra E. Katzen, B.S.
Polly E. Raith
Rebecca J. Torrence

The following members from other departments and divisions have joint appointments with the Biomedical Computer Laboratory to facilitate collaboration and enhance interdisciplinary research:

G. Charles Oliver, M.D., Associate in the Biomedical Computer Laboratory, Professor of Medicine and Chief of Cardiology, Jewish Hospital
Rexford L. Hill, M.S., Research Associate in the Biomedical Computer Laboratory and Assistant Professor of Computer Applications in Radiology
John W. Lewis, Ph.D., Research Associate in the Biomedical Computer Laboratory, Assistant Professor of Pathology and of Electrical Engineering, and Director of Laboratory Computing, Barnes Hospital
Carol S. Higgins, A.B., Research Assistant in the Biomedical Computer Laboratory and Research Associate in Radiology

In addition, the following people worked at the laboratory for brief periods:

Jeffrey D. Coe, B.S.
Rick M. Cox, M.S.
Mary L. Dunne, B.S.
Markku T. Hakkinen
Gail S. Kuthe, B.S.
Regis G. Lagler, M.S.
Ross D. Livengood, B.S.
Raymond E. Martin, Jr.
Ross E. Morgan, B.S.

Arthur Y. Ng
Donald A. Opila, B.S.
Thomas F. Schuessler, B.S.
John B. Schweitzer, B.S.
Paul B. Webb
Jeffrey V. Winston, B.S.

RESEARCH COLLABORATORS

During the period covered by this report the following investigators from other laboratories, departments, or institutions, collaborated with BCL staff members on problems of joint interest.

J. Achtenberg, A.B., Medicine
G. G. Ahumada, M.D., Medicine
W. E. Ball, D.Sc., Computer Science
L. J. Banaszak, Ph.D., Biochemistry
C. D. Barry, Ph.D., Computer Systems Laboratory
R. W. Beauchamp, Cardiothoracic Surgery
B. Becker, M.D., Ophthalmology
R. J. Benson, J.D., Computing Facilities
W. F. Boron, Ph.D., Physiology and Biophysics
S. B. Boxerman, D.Sc., Health Care Administration
J. D. Byrne, CPT, Medicine
M. K. Campbell, R.N., Medicine
C. Chi, M.S., Neurology
G. L. Clark, M.D., Medicine
R. E. Clark, M.D., Cardiothoracic Surgery
P. B. Corr, Ph.D., Medicine and Pharmacology
C. M. Currie, B.S., Radiology
A. A. Ehsani, M.D., Medicine
J. O. Eichling, Ph.D., Radiology
D. L. Elliott, Ph.D., Systems Science and Mathematics
R. A. Ellis, M.S., Computer Systems Laboratory
R. G. Evens, M.D., Radiology
C. Frieden, Ph.D., Biochemistry
M. H. Gado, M.D., Radiology
E. M. Geltman, M.D., Medicine
T. A. Gillespie, M.D., Medicine
S. A. Golden, B.S., Neurological Surgery
S. Goldring, M.D., Neurological Surgery
R. S. Gordon, B.A., Health Care Administration
K. S. Gowda, M.D., Medicine
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R. L. Grubb, Jr., M.D., Neurological Surgery
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A. Hernandez, M.D., Pediatrics
J. Hirsch, B.S., Medicine
J. O. Holloszy, M.D., Preventive Medicine
S. R. Holmes, B.S., Biochemistry

J. T. Hood, B.S., Physics
C. P. Hughes, M.D., Neurology
S. Igielnik, Ph.D., Medical Computing Facilities
C. M. Jackson, Ph.D., Biochemistry
L. Jarett, M.D., Pathology
G. C. Johns, B.S., Computer Systems Laboratory
M. F. Johnson, Jr., M.L.S., Medical Library
R. G. Jost, M.D., Radiology
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S. A. Kahn, Electrical Engineering
R. P. Karlsberg, M.D., Medicine
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S. Lang, Ph.D., Physiology and Biophysics
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J. L. Livingston, A.B., Ophthalmology
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R. E. Marshall, M.D., Pediatrics
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Worcester Polytechnic Institute, Worcester, Massachusetts

C. L. Feldman, Ph.D.

Previous years have seen occasional collaborative efforts with various computer firms and equipment manufacturers. This year projects of joint interest have involved:

Artronix, Inc., St. Louis, Missouri - The MUMPS information system.

Mennen-Greatbatch, Clarence, New York and Hewlett-Packard, Waltham, Massachusetts - An arrhythmia monitoring system.

Picker Corporation, Cleveland, Ohio - A reconstructive X-ray tomographic system.

Sandoz-Wander, Inc., Hanover, New Jersey - A collaborative drug study.

IV. PHYSICAL RESOURCES

On April 15, 1964, the Biomedical Computer Laboratory was formed and the original staff moved into 5,515 square feet (gross) of laboratory space at 700 South Euclid Avenue, just across the street from the main building of the Washington University School of Medicine. During the past eleven years the laboratory space has been increased by 1526 square feet in the basement, 2762 square feet on the ground floor, and 3891 square feet on the second floor of 700 South Euclid, and by 3463 square feet on the second floor and 1257 square feet in the basement of the building just south of the original space. The added space includes 720 square feet created by enclosing a porch on the second floor of 700 South Euclid in the Spring of 1976. The gross total is now 18,000 square feet. Facilities for computational applications, laboratories, staff offices, and a WUCL reference room occupy the various BCL spaces. Other laboratory facilities include a well-stocked electronics shop, a large inventory of electronic and computer test equipment, a variety of digital system modules, and both analog and digital tape recorders.

Frequently it is appropriate for computer systems to be housed physically near areas of clinical application. On October 1, 1969, an on-line computer monitoring system was installed by BCL in the Cardiac Care Unit of the Barnes Hospital complex. The computer equipment was housed in 360 square feet of specially designed space within the unit. This system supported routine clinical monitoring and research until mid 1975 when it was replaced by a commercial version built by Mennen-Greatbatch, Inc. A computer-based Surgical Intensive Care Monitoring System designed and built by BCL was installed in Barnes Hospital in March, 1973. The computer and related hardware are located in a room within the intensive care facilities.

Throughout the years the laboratory has steadily increased its computational capabilities with the addition of new computer systems. At the time the laboratory was formed, equipment then available for laboratory applications of digital computers was a single LINC (Laboratory Instrument Computer). This small stored-program computer had been designed specifically for use in biological and medical laboratories where there is a requirement for strong coupling between the computer, the investigator, and other experimental equipment. Since that time some twelve LINC's and five PDP-12's, a newer implementation of the LINC, have been added to the resources of the Washington University medical community.

In 1966 the Programmed Console was designed at BCL to function as a combined stored-program digital computer and remote display console for the IBM System/360 Model 50 installed during May, 1966, at the Washington University Information Processing Center. (The Model 50 was converted to a Model 65 in April, 1973.) BCL's computational facilities now include three specialized Programmed Consoles built at the laboratory. In addition, thirteen Programmed Consoles have been built by SPEAR, Inc., from plans and specifications developed at BCL. Of these, six

were evaluated under an NIH sponsored program as an aid to radiation treatment planning at radiology centers in Stanford, California; Bethesda, Maryland; Houston, Texas; Boston, Massachusetts; Philadelphia, Pennsylvania; St. Louis, Missouri; and Toronto, Canada. Two Programmed Consoles manufactured by SPEAR, Inc., are in use in other projects at BCL. In 1972 five new PC-1200 Programmed Consoles manufactured by Artronix, Inc. were installed at BCL in support of a variety of new and existing projects. All of the evaluation centers, except that at Toronto, Canada, have now replaced their SPEAR PCs with new Artronix PC-1200 systems. The SPEAR PC in the Cardiac Catheterization Laboratory was replaced in 1973 by a new Artronix PC-1200 System housed in newly renovated space for Catheterization Laboratory Instrumentation, and in 1974 an Artronix PC-12/7 MUMPS System was installed at BCL, to be used in a variety of projects in Health Care Technology and information systems.

An IBM System/7 was installed at the laboratory in April, 1972 to become a major component of a system for high-speed analysis of electrocardiograms. (A second IBM System/7 was leased from November, 1973 to November, 1975.) 1972-73 also marked the beginning of routine use of the inventory of macromodules for significant work supporting research in hearing and speech, high-speed ECG processing, and higher-level-language performance improvements.

In May, 1973, a Texas Instruments TI-980A computer was acquired which is being used as a major element in a satellite patient-monitoring system. A TI-980B computer system was added in December, 1974, to be used in program development, microprocessor support, and booster cart system development, and two additional TI-980B computers were acquired in 1975, one to support patient monitoring software development and the other to serve as a component of an MMS-X graphics system.

In September, 1975, two CALDATA 135 computers and associated peripherals began service in the development of a system for high-speed ECG processing with functions similar to those of Argus/H implemented on the IBM System/7 but with improved performance at a lower cost.

A survey of computer systems installed at the Washington University Medical Center shows nearly one hundred minicomputer systems, with twenty different makes and models represented, applied to diverse clinical and research areas. In addition, microprocessors are being used in increasing numbers both in special instruments built at the laboratory as well as in commerical instruments.

V. RESEARCH PROJECTS

Introductory Summary

The goal of the Laboratory is the application of computer techniques to problems in medicine and biology. The Laboratory's research program has traditionally been organized into several major project areas with the staff grouped into teams whose interests are focused correspondingly.

As in past years, project groupings have been modified to reflect evolving patterns of research activity. "Tomography Systems" is a new section which brings together continuing projects in positron-emission transaxial tomography (PETT) with emerging work in ultrasonic tomography. Development of the PETT systems has been reported previously under "Tracer Kinetics." Other projects employing tracer techniques are grouped now according to their biomedical emphasis. Early explorations into ultrasonic tomography were introduced last year under "Supporting Activities." A new title, "Central Nervous System Diseases and EEG Analysis," embraces some of the work from "Tracer Kinetics" along with new collaborations between the Laboratory and the Department of Neurology and Neurological Surgery. In the area of Information and Communications Systems, our longstanding activities have contributed to the establishment of an Information Systems Group (ISG). Last year ISG became administratively distinct in order to recognize its central direction by the chairman of the Department of Computer Science, Dr. Jerome R. Cox, Jr., as well as to accommodate flexibly the strong collaborative ties with both the Computer Systems Laboratory (CSL) and the Biomedical Computer Laboratory (BCL). Work specifically related to ISG is reported under separate cover whereas BCL's growing involvement in database applications is now addressed in "Databases for Disease Management and Research."

Within those project groupings which continue from prior years, more subtle shifts in direction have evolved. Work related to "Ischemic Heart Disease and ECG Analysis" continues to emphasize high-speed analysis of long-term recordings with increasing attention being given to analysis of a maturing database which addresses the natural history of sudden death. Other prominent activities are in support of the Division of Cardiology's SCOR program and of a new collaboration with the American Heart Association to establish a database for evaluating arrhythmia analysis systems. The title, "Clinical Pathophysiology and Patient Monitoring," replaces "Monitoring the Critically Ill" to better reflect increasing attention to the development of systems and devices for pathophysiologic research. Projects reported under "Cardiac Catheterization Laboratory" continue to focus on a second-generation data acquisition and analysis system for physiologic signals as well as on an advanced system for processing ventricular angiographic images. In the area of "Laboratory Biochemistry," microprocessor applications to problems in biochemical instrumentation are showing increasing prominence. Implementation of the previously reported model of cochlear mechanics has brought new dimensions to our diverse collaborations with the Central Institute for the Deaf in the area of "Speech and Hearing."

Individual Projects

A. Ischemic Heart Disease and ECG Analysis

The projects reported in this section continue longstanding work in real-time and high-speed ECG analysis. Many of the clinical studies detailed below are natural outgrowths of the ECG analysis work, as are the strong interests in the evaluation of automated arrhythmia detectors. Modeling and signal-processing endeavors in the field of cardiology have taken the form of collaborations which address other aspects of ischemic heart disease, such as the kinetics of enzyme release and the electrophysiologic characterization of abnormal myocardial depolarization. Digital techniques applied to clinical echocardiography are reported here, whereas other ultrasonic work applied to tomography is considered in section B.

Argus/H is a high-speed version of the real-time computer-based arrhythmia monitoring system, Argus, which was in operation in the Barnes Hospital Coronary Care Unit (CCU) from 1969-1975 and replaced in 1975 by "Argus/Sentinel," a commercially available version developed through collaboration with the Mennen-Greatbatch Company. Work on Argus/H was begun in 1971. It has since matured to a heavily used system for processing 24-hour recorded ECGs at sixty times real time. Although the principal application of Argus/H continues to be the study of ventricular dysrhythmias in ambulatory patients who have survived a myocardial infarction, there are rapidly increasing interests here and elsewhere in utilizing such systems for therapeutic trials of antiarrhythmic agents as well as for evaluation of interventions designed to protect the ischemic myocardium. Argus/H is especially valuable for such studies because of its ability to yield precise quantitative measures of significant ventricular arrhythmias.

Argus/H employs specialized hardware (macromodules) to encode ECG data sampled at 15,000 samples per second. Software and appropriate peripherals expedite review and edit of computer results which are saved for subsequent statistical analysis via the University's IBM 360/65. Extensive evaluations have verified the integrity of the analysis algorithm, proven the value of the quantified results as compared to conventional manual-scanning techniques, and confirmed the consistency of results on reprocessing. Recent work has developed a post-Argus processing stage which uses more contextual information to substantially improve system efficacy. A new system, Argus/2H, is designed to capitalize more fully on new algorithms, to provide for dual-channel processing, and to allow graceful exportation of the system. Argus/2H will be applied locally to production processing of Holter ECGs for study of the natural history of sudden death, it will provide the power and flexibility necessary for work on new signal-processing strategies, and it will serve the analysis and documentation needs of the nationally-directed work to generate an annotated digital database for the evaluation of automated arrhythmia detectors.

A-1. Algorithms for High-Speed ECG Processing

Personnel: C. N. Mead, BCL
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Support: RR 00396
HL 18808

Argus/H algorithm development during the past 2 years has centered around efforts to reduce the amount of time a trained technician (editor) must spend reviewing and validating PVCs identified by the computer during Argus processing. During the past year an algorithm for automatic confirmation of most isolated-PVCs (initially presented in PR 12 (A-15)) was extensively evaluated and is now in routine use.(1) Briefly, the algorithm (machine edit) consists of 3 separate processing stages, all of which operate on Cycle-stream data following Argus processing. 1) SET-UP: The Cycle-stream is searched and all family members of all beats called PVC by Argus are recorded in a catalog (PVC Catalog). In addition, the number of PVCs in each family is saved. 2) SORT: Beginning with the largest family in the PVC Catalog, the coupling interval (CI) for all members of the family is calculated and the list of CIs analyzed for the relationship of the family's average CI to the average R-R of the tape. The consistency of individual members of the CI list is checked also. 3) LABEL: All families considered PVC families on the basis of SORT criteria are used to generate clusters based on the four Argus morphological measurements. The Cycle-stream is then searched for all beats which are members of one of the machine-generated clusters. Such beats are automatically labeled true-PVC if their CI in both the forward and backward directions is appropriate.

The machine edit algorithm was evaluated on 24 tapes from 24 different patients with an average recording period of 9 hours, 44 minutes. All tapes had been previously edited by a trained technician and the edited data were used as the standard for comparison. Tapes were selected on the basis of having more than 200 Argus identified PVCs. The machine edit algorithm correctly identified 94.8% of all isolated true PVCs. No attempt was made to label as false PVCs those beats incorrectly called PVC by Argus. In addition to the true PVC detection accuracy noted, the machine edit strategy identified twice as many missed PVCs as the human editor.

(1) C. N. Mead, K. W. Clark, G. C. Oliver, and L. J. Thomas, Jr., "Progress Toward Fully Automated Processing of Ambulatory ECGs," Proceedings of the Conference of Computers in Cardiology, IEEE Catalog No. 76 CH 1160-1C, St. Louis, Missouri, pp. 183-188, October 7-9, 1976.

A-2. Argus/2H: Hardware

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Support: RR 00396
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All hardware for the Argus/2H system has been installed. The system is currently implemented with two Cal Data 135 processors; but for purposes of exportability, interfaces are completely compatible with the PDP-11 processor series. Since the last report (PR 12, A-16) several hardware additions have been made: (1) the high-speed strip chart recorder was upgraded from two channels to four, (2) a programmable real-time clock was added, (3) the dual-density nine-track tape system was installed, (4) the direct memory access interface to the high-speed display oscilloscope was designed and built. Currently, plans are underway to double the capacity of the disk system by upgrading to high density Control Data 9762 storage module drives. This will lower software overhead by eliminating the need to pack and unpack ECG data on the disk.

A diagram of the system is shown in Figure 1. In addition to the dual processors, standard peripherals include CRT terminals, line printer, real-time clock, cartridge disk, and parallel digital input-output ports. Special peripherals include: (1) a dual-channel direct memory access analog-to-digital converter for on-line data acquisition with minimum processor loading, (2) storage module disk drives for random access storage of 24 hours of two-channel ECG data, (3) a high-speed strip-chart recorder for producing annotated ECG strips, (4) an 800/1600 bit per inch nine-track tape system for archival data storage, (5) a high-speed direct memory access display oscilloscope for display without refresh flicker. The display operates in four different modes for X-Y, character, ECG, and vector display.

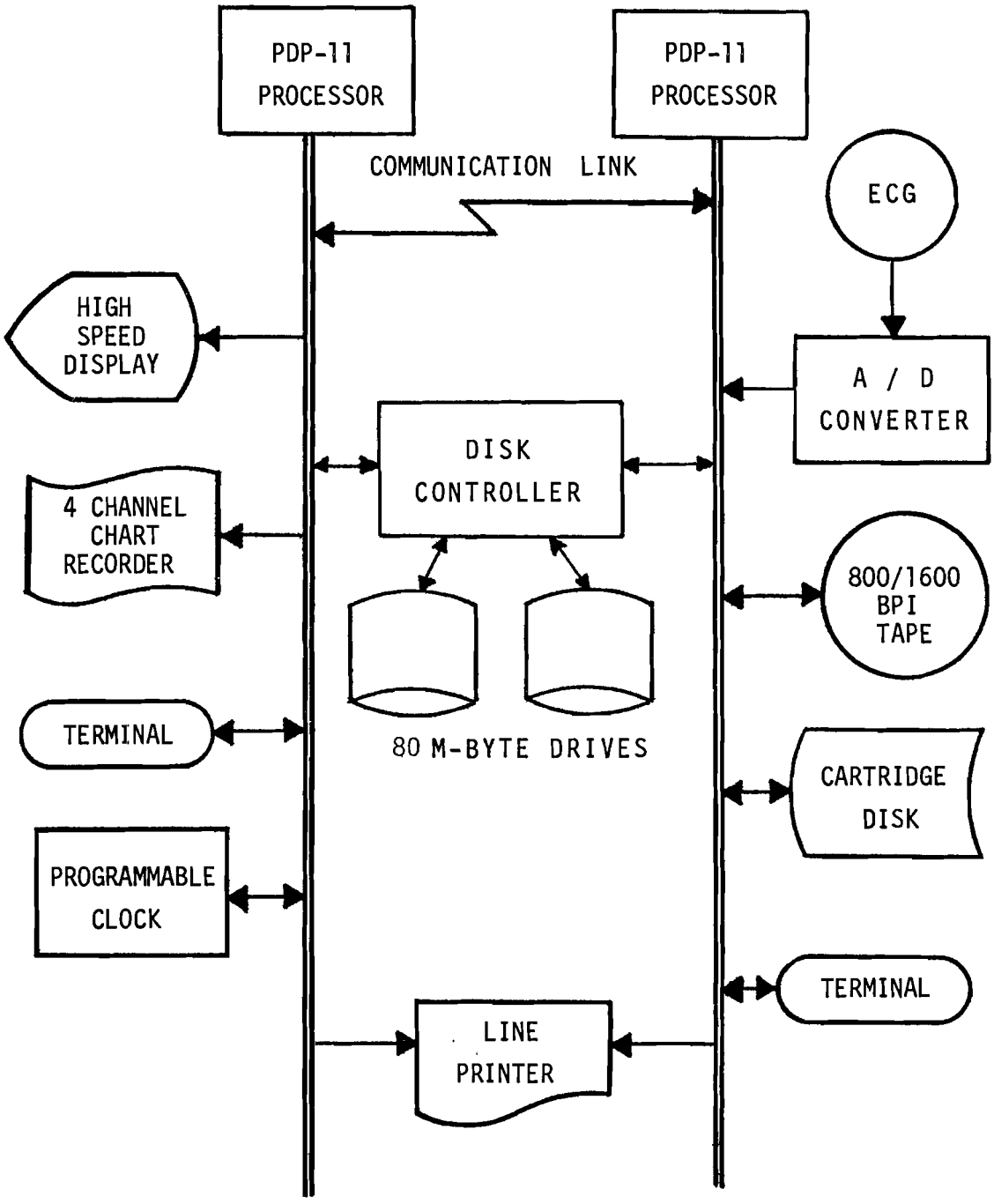

Figure 1. Argus/2H hardware schematic.

A-3. Argus/2H: Software

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Sufficient software for Argus/2H has been written to permit the processing of dual channel 24-hour Holter recordings. Full operation has been temporarily postponed until the disk mass storage system has been augmented to double capacity (A-2). The software operating system is a locally modified DEC RT-11; application programs have been written in a combination of assembly language with RT-11 system macros and RT-11 FORTRAN.

The ECG acquisition program accepts 256-word blocks of digital samples from the hardware FIFO buffer (A-2). Samples from the two channels appear in alternate words. When a 4K software buffer is filled, differences between successive samples are computed. Channel one and channel two differences are packed into one word. Buffers of 2K first differences are transferred to the disk storage module with actual sample values interspersed each 256 words. The rate of digitization is 60 times the real time rate of 250 samples per second per channel.

The Argus/H rhythm analysis algorithms of Aztec, Primitive, and Cycle have been translated for Argus/2H. The algorithms were unchanged except for the output Cycle stream which now includes individual beat features (duration, height, offset, area). For Argus/H, only family cluster features were saved. Either channel may be scanned with these algorithms.

An edit program has been written, which includes all features of the Argus/H edit program (PR 11, A-11) and the following additional features: (1) the second channel is available for display at any time, (2) the onset of any beat may be adjusted, (3) before exit from the program the editor is obligated to view the shortest and longest coupling intervals for non-PVC to PVC, PVC to PVC, and normal to normal, (4) special displays of normal to normal (NN) and NN difference histograms are available to help assess the incidence of supraventricular arrhythmias, (5) ECG strips include 4 channels (two channels of signal, one for Cycle labels, and one for time markers). While ECG strips are typically 8 and 16 seconds in length, strips of any length are available.

Hard-copy summary outputs include: (1) gross summary of tape characteristics and editing decisions, (2) heart-rate and PVC-rate plots over time, (3) histograms of NN intervals, NN differences, non-PVC to PVC intervals

and logarithms of intervals of PVC to PVC without regard to intermediary beats, (4) histograms of ratios of N_1N_2/N_2V and VN_3/N_2V for beat sequences $normal_1$, $normal_2$, PVC, $normal_3$, (5) detailed coupling interval information for each couplet and run, (6) histogram of coupling intervals of non-PVC to PVC over time. The machine-readable Cycle stream is saved on tape with other Cycle streams for subsequent statistical analysis (A-6).

A variety of utility programs has been written to supplement those of the operating system and to facilitate application programming. Included are non-file-structured disk-to-tape, tape-to-disk, and disk-to-disk routines. A Cycle-compare program facilitates comparison of two disk-resident Cycle streams; the program is a necessity for testing algorithm changes and verifying translations of programs from Argus/H. A file-structures save/recovery program facilitates back-up program maintenance on a user-by-user or on a system basis. Disk and tape dump routines also are available. Diagnostic programs have been written for troubleshooting the high-speed scope controller, chart recorder controller, and A/D signal acquisition system (A-2).

A-4. Holter Tape Processing

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In conjunction with the study of ventricular arrhythmias and sudden death or "core project study" (PR 11, A-1; A-7), all processable 10-hour Holter recordings from 327 patients, obtained during their first year following infarction (9 tapes scheduled per patient), have been analyzed by Argus/H on the IBM System/7 from 1973 to 1977. However, since a new editing protocol was instigated in 1975, several hundred of these recordings which were edited under the original protocol are being "re-edited" under the new protocol to align the resultant database of Cycle streams.

For the new natural history study (PR 12, A-1) 667 twenty-four-hour tapes have been analyzed by Argus/H. These tapes have top priority and are analyzed, for the most part, within 48 hours of receipt. Other studies which have used the Argus/H system include interventions designed to protect the ischemic myocardium immediately after infarction, antiarrhythmic drug trials, the incidence of PVCs in patients on kidney dialysis (A-9), and the effect of propranolol on the incidence of ventricular arrhythmias in patients with mitral-valve prolapse syndrome, the analysis of which is now in progress.

The machine-edit algorithms (A-1) were implemented in late 1976 and have reduced considerably the amount of editing time for tapes with more than a few hundred PVCs. The value of these algorithms has been especially noteworthy in a pilot study of the efficacy of LB-46, a cardioselective beta-blocking agent developed by Sandoz-Wander, Inc. For that study in particular, PVC rates of over 1000 per hour are commonly encountered.

The machine readable beat-by-beat summary (Cycle stream) resulting from Argus/H processing is saved on a magnetic tape which, when full, is forwarded to the IBM System/360 (A-6) where each Cycle stream is condensed into 154 variables chosen for their relevance to current research interests.

A-5. LSI-11 Argus/RT

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In response to the need for a low-cost ECG rhythm monitor the development of a microcomputer-based system has been undertaken. The Digital Equipment Corporation LSI-11 was chosen for software compatibility with other members of the PDP-11 family for which there exists proven ECG rhythm analysis software. In addition, the ongoing development of a PDP-11 based high-speed ECG analysis system (A-2, A-3) provides a convenient support system for the smaller machine.

Several innovative schemes have been incorporated into the new system. All programs are stored in read-only memory, eliminating the need for secondary storage for program backup or a connection to a host system capable of bootstrapping the smaller system. An automatic gain control algorithm developed for use in the SICU (C-1) has been condensed for use within the Primitive portion of the Argus algorithms. This algorithm varies the slope parameters used by Primitive for QRS acceptance based on a running average of QRS amplitude. It provides improved immunity to signal noise and decreases the false recognition of large amplitude P-waves and T-waves as QRS complexes.

A further improvement in T-wave recognition has been added, which provides a simple method of correctly classifying more than 90% of the T-waves of sufficient amplitude to pass the stricter QRS acceptance parameters.

Heart rate, arrhythmia count, and other parameters may be continuously displayed on an alphanumeric panel display. If any of a number of alarm conditions is encountered, a pertinent alarm message is displayed and a strip of ECG, with patient identification and rhythm annotation, is generated. Sufficient read-write memory has been provided to store 16 seconds of ECG data for replay when an alarm condition is encountered.

The LSI-11 Argus/RT system is compactly packaged to afford portability. Interfaces have been constructed to allow acceptance of data from the ECG telemetry system in the SICU (C-9) or from an analog-to-digital conversion subsystem. This will allow the LSI-11 to be transported to any location where it is required without the need for cumbersome peripheral devices.

A-6. Extended Analysis of Argus/H-Quantified Ventricular Ectopic Activity

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Following the processing and editing of Holter tapes by Argus/H or Argus/2H (A-3, A-4) the beat-by-beat annotation of the 10- or 24-hour recordings (Cycle streams) are accumulated on industry-compatible tape and transported to the IBM System/360 for bulk processing of the Cycle streams in order to extract salient features of the ventricular ectopic activity (VEA).

Summary (PR 12, A-2), a PL/I program running on the IBM System/360, reduces the beat-by-beat annotation of the Holter tape to 154 variables chosen for their relevance to current clinical research interests.[1] The output from Summary then is passed as input into a SAS program (D-17) for analysis of the resultant data and its merging with relevant clinical information obtained through the MIPI system (D-2). The results of the Cycle-stream processing are merged with the information obtained from the cardiologic review process. A MUMPS database maintained as part of the MIPI system (PR 12, A-1) assists in the management of this library of Cycle streams and abstracted information.

The current list of variables available for analysis includes pertinent identification data, date of edit, and duration of the recording. PVCs are characterized in several ways, reflecting current research interests. First, general characteristics are recorded, such as the total number of PVCs, their average QRS duration, and the $\log_{10}$ of the average PVC rate per hour. More detailed information is provided about the earliest PVC (the PVC with the shortest coupling interval). For specific classes of PVCs of interest more detail is abstracted, including average coupling interval (in ms) and the frequency distribution of the coupling intervals. The current classes of PVCs of interest are those which start a couplet or run, those within a salvo, and those both preceded and followed by non-PVCs. For each tape, salvos (couplets or runs) are further characterized by frequency distribution of the number of salvos at each ventricular rate and the longest run at each rate. Finally, detailed information about the heart rate based on average normal-to-normal intervals for each five minute period is computed.

The value of Summary became evident in investigation of the coupling intervals of the initiating beats of salvos of PVCs. We had previously reported(2) that, contrary to conventional wisdom, couplets and runs usually were initiated by late PVCs, but the number of couplets and runs available for analysis was rather small. To examine the question more thoroughly we utilized SAS to analyze 953 tapes which were recorded from 295 patients two weeks to one year after myocardial infarction. Of these tapes, 197 had one or more couplets and 63 had one or more runs. For each tape, the cumulative distribution of PVCs with respect to their coupling intervals was computed, both for isolated PVCs (those which were not part of a salvo) and for the beat initiating a couplet. The distribution of beats was found to be slightly, but consistently, later for those initiating a couplet. For each tape an average coupling interval was computed for isolated PVCs and also for PVCs initiating a couplet. These were then averaged over the 197 tapes. The initial PVC of a couplet had an average coupling interval of 498 ms, while the average isolated PVC on those same tapes averaged 485 ms. In 102 of the 197 tapes (52%) the average coupling interval of the beat initiating the couplet was greater than the average coupling interval of isolated PVCs on that tape.

This trend was even more pronounced for beats initiating a run (3 or more consecutive PVCs). The initial PVC of a run had an average coupling interval of 567 ms compared with 484 ms for isolated PVCs on the same tapes. In 42 of the 63 tapes (67%) the average coupling interval was longer for PVCs initiating runs than for isolated PVCs. Thus, although it may be true experimentally that early PVCs may be more likely to lead to ventricular fibrillation, naturally occurring salvos usually are not initiated by early PVCs.

A second example demonstrates the power of the new scheme for the evaluation of therapeutic interventions such as drug therapy. One of the problems plaguing investigators of antiarrhythmic drugs has been the variability of responses exhibited by individual patients when measured by using simple PVC frequency or severity of VEA observed on and off of antiarrhythmic agents. The increased quantification afforded by the new Argus/H scheme has allowed examination of more subtle parameters as response variables for drug evaluations.

In a recent cross-over, double-blind study of 10 patients the effects of placebo, phenytoin (100 mg. qid), procainamide (500 mg. qid), and quinidine (300 mg. qid) were compared. While an analysis of simple PVC rates showed that each agent was effective for some patients and that at least one agent was effective for each patient, the results did not suggest the manner in which the drugs were effective. The recently implemented analysis scheme has allowed us to detect a reliable coupling-interval-dependent effect of the drugs. During quinidine treatment the distribution of coupling intervals was shifted toward longer intervals, while the opposite effect was observed for phenytoin. These effects are consistent with the known physiological actions of the drugs on myocardial tissue. Other analyses reported elsewhere (A-7, A-8) also have utilized the resulting database.

Currently work is progressing in an attempt to understand the relationship between the variables extracted for analysis and the judgments made by the cardiologists during the review process about the existence of early PVCs. Early PVCs are defined as PVCs which begin during or immediately adjacent to the T wave of the preceding beat. This measurement cannot presently be made by Argus as current Argus algorithms are unable to reliably detect T waves. Physiologically the QT interval varies both across individuals and within an individual as a function of heart rate, making the coupling intervals currently measured by Argus imprecise indices of this judgment.

The reviewers independently judge whether or not an early PVC is present on the tape, and if there is none, whether or not there is a middle PVC (i.e. one beginning within 40 ms of the T wave of the previous beat), or, in the absence of either, that all PVCs are late. Previous experience has indicated that even this crude judgment was an important predictor of subsequent sudden death, but that the degree of disagreement among cardiologists was significant. Reasons for the disagreement were due both to oversights and to differences of judgment when the T wave was not clearly demarcated because of noise or low amplitude.

Tapes in which the first two reviewers agreed on the early classification were selected for study and a variety of univariate and multivariate techniques were utilized in an attempt to predict the reviewers' judgments. The single variable which most closely predicts is a calculated index in which the coupling interval of the PVC with the shortest coupling interval is divided by an estimate of the QT interval computed from an average heart rate in the vicinity of the earliest PVC by a formula given by Ashman.[3] The results are summarized in Table I. No other variables investigated were able to appreciably improve the prediction. Further refinement of the index may be possible by identifying the PVC with the lowest index instead of using that with the shortest absolute coupling interval, by refinement of the heart rate utilized to compute the QT (e.g. running average, beat just prior to PVC), and possibly by correcting for interpatient differences by utilizing the QT interval from the 12 lead ECG currently obtained at the time of the recording. In order to facilitate the refinements, Summary will be revised to extract detailed information about current heart rate for each PVC and to create a new database which will contain the relevant information for each of the 0.66 million PVCs currently analyzed. Future analyses will focus on the relationship of this earliness index to other characterizations of the VEA and its power in predicting subsequent sudden death.

Table I

Relation of Early Index to Cardiologist Judgments

Early Index	Cardiologist Judgements: Early	Middle	Late
< 1	65	11	52
1.0-1.1	18	6	132
> 1.1	2	5	323

(1) J. P. Miller, J. A. Ritter, K. W. Clark, L. J. Thomas, Jr., and G. C. Oliver, "Extended Analysis of Argus/H Quantified Ventricular Ectopic Activity," Proceedings of the IEEE Conference on Computers in Cardiology, IEEE Catalog No. 76 CH 1160-1C, St. Louis, Missouri, pp. 165-170, October 7-9, 1976.

(2) R. E. Kleiger, T. F. Martin, J. P. Miller, and G. C. Oliver, "Ventricular Tachycardia and Ventricular Extrasystoles During the Late Recovery Phase of Myocardial Infarction," American Journal of Cardiology, vol. 33, p. 149, 1974 (abstract).

(3) R. Ashman, "The Normal Duration of the Q-T Interval," American Heart Journal, vol. 23, pp. 522-534, 1942.

A-7. The Natural History of Sudden Death

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Patients recovering from myocardial infarction (MI) may have strikingly different PVC rates during the early recovery period, depending upon whether or not they had cardiomegaly (CM), a non-inferior infarction or a high peak serum glutamic-oxalacetic transaminase (SGOT) during their sojourns in the coronary care unit (PR 12, A-3). Five clinical groups were found who displayed, three months after infarction, marked differences in PVC rates affirmed by Argus/H analyses of Holter recordings.

Because of the relationship between ventricular ectopic activity and sudden death, we have followed these patients to determine their subsequent fates. We defined "sudden death" as death within one hour of the onset of symptoms. The definition of each group, their 3-month average PVC rate, and mortality experience are summarized below.

One Year Mortality

Group	I	II	III	IV	V
ECG location	non-inferior	non-inferior	inferior	non-inferior	non-inferior
CM	+	+	+ or -	-	-
Peak SGOT	$\geq$ 240	< 240	any	$\geq$ 120	< 120
N	18	44	121	18	17
3 mo. avg. PVC rate	32.4	5.0	2.8	1.7	0.2
Sudden Death #, (%)	3,(17)	3,(7)	5,(4)	0,(0)	1,(6)
Non Sudden Death #, (%)	3,(17)	3,(7)	10,(8)	1,(6)	2,(12)
Total Mortality #, (%)	6,(33)	6,(14)	15,(12)	1,(6)	3,(18)

The high death rate (both sudden and non-sudden death) for clinical group I is noteworthy ($p<0.02$) and further suggests a relationship between ventricular arrhythmias occurring during the early recovery period of myocardial infarction and subsequent one-year mortality.

A-8. PVC Frequencies During One-Year Followup After Myocardial Infarction

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Now that the processing of the Holter tapes for a previous natural-history study is nearing completion (A-4) we have examined the Argus/H quantified PVC rates for all 295 patients who were part of that study (Table I). The PVC rates at the two-week in-hospital recording are clearly depressed below those observed on an outpatient basis and studies are underway to elucidate this relationship. At three months the rates again seem to increase slightly and by four months appear to reach a plateau. The relationship of these group averages to the individual patient patterns continues to be of interest, particularly in light of the previously described (PR 11, A-7), observation that about one-third of the patients showed a marked increase in PVC frequency at six to nine months after myocardial infarction (MI). That study considered a subset of only 20 patients and currently is being extended to the observations of the larger group of patients.

The PVC rates observed are highly intercorrelated, as shown in Table II. The correlations generally are stronger as time progresses post-MI and for tapes closer in time, but the effect is not strong and the two-week tape correlates almost as strongly to the twelve-month tape as it does to the one-month tape. The analyses reported here ignore problems of dropouts and end points reached during the first year. Since the 56 patients for whom all nine recordings are available demonstrate generally lower PVC rates, the adjustments for the large number of missing values await the development of more sophisticated analytic models.

Table I

PVC Rates (per hour) During the First Year Following Myocardial Infarction

Recording Session	N	% with PVCs	Average* PVC Rate	Median PVC Rate	75th Percentile	90th Percentile
2 wk	242	76	.86	.59	4.22	28.24
1 mo	210	84	1.65	1.33	10.97	46.07
2 mo	235	80	1.71	1.30	15.98	64.21
3 mo	208	81	1.91	1.47	15.83	75.34
4 mo	195	84	2.53	2.48	25.00	89.77
5 mo	193	82	2.74	3.47	26.20	82.90
6 mo	192	81	2.56	2.37	26.46	99.27
9 mo	177	89	3.07	3.44	25.18	103.94
12 mo	168	85	2.67	3.65	19.16	86.10

*Based on the log transform of $\left(\frac{\#\text{ of PVCs} + .5}{\text{Data loss corrected tape length}} \right)$

Table II

Correlations* of PVC Rates During the First Year Following Myocardial Infarction

	2 wk	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	9 mo
2 wk	1.00							
1 mo	.45	1.00						
2 mo	.52	.49	1.00					
3 mo	.41	.51	.66	1.00				
4 mo	.35	.45	.58	.76	1.00			
5 mo	.43	.53	.55	.73	.69	1.00		
6 mo	.42	.38	.61	.68	.68	.80	1.00	
9 mo	.30	.50	.53	.58	.51	.61	.67	1.00
12 mo	.42	.43	.44	.62	.58	.68	.64	.64

*Product moment coefficients based on log transform of PVC rates. All correlations are significant ($p < .001$) and are based on all available pairs.

A-9. Analysis of Longterm ECGs Taken During Hemodialysis

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Patients with end-stage renal disease (ESRD) have a high incidence of coronary artery and hypertensive cardiovascular disease which, in turn, are associated with increased frequency of ventricular ectopic activity (VEA). Even though the electrolyte and acid-base shifts produced by hemodialysis might be expected to alter VEA, the effects of hemodialysis on the incidence, severity, and stability of VEA have not been characterized. Fifteen patients were studied by analysis of 24-hour Holter recordings started four hours prior to and continued for sixteen hours following a four-hour period of dialysis. Four patients had Holter recordings taken continuously for five days. Electrolyte and blood gas determinations were done for all patients before, during, and after dialysis. Most patients were being treated with antihypertensive drugs, including propranolol. Standard ECGs were normal for two-thirds of the patients, but evidenced left ventricular hypertrophy in the others. Although the standard ECGs showed no VEA, the Holter recordings from fourteen patients (93%) showed PVCs which were multiform in eight (53%) while four patients (27%) exhibited runs of ventricular tachycardia (VT). The latter is five times the frequency of VT commonly encountered in the post myocardial infarction period. Three of the four had ventricular rates exceeding 100 per minute in their VT episodes. No temporal relationship was found between VEA and the pre-, intra-, and post-dialysis periods in spite of dramatic changes in electrolytes and acid-base balance. These observations suggest that hemodialysis does not aggravate the VEA which is strikingly frequent in patients with ESRD and may contribute to their high mortality from cardiovascular disease.

A-10. Influence of Clinical Features of Acute Myocardial Infarction on Ventricular Tachycardia Two Weeks to One Year Following Infarction

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Ventricular tachycardia, i.e. runs of three or more consecutive PVCs, has received considerable attention as a risk marker for subsequent sudden death. Patients who were admitted to the Barnes and Jewish Intensive Care Units with the diagnosis of a definite myocardial infarction (MI) during the period between November, 1971, and June, 1975, and who were subsequently monitored at two weeks, monthly to six months, and then every three months to one year following their MI (PR 11, A-1), were utilized to explore the degree to which features observed during the acute phase of their MI would predict the presence of runs on Holter tapes during the first year following their infarct.

The clinical features information was coded on special forms,(1) keypunched, and entered into a SAS database (D-17). This information then was merged either with keypunched summaries of Argus processing and subsequent review or with the results of the IBM System/360 processing of the Argus produced Cycle streams (A-6). The percentage of tapes demonstrating at least one run for each recording session is depicted in Table I. The depressed

Table I. Percent of Tapes Showing at Least 1 Run
2 Weeks to 1 Year Following MI

Recording Session	N	% with runs
2 wk	237	2.95
1 mo	209	11.48
2 mo	232	10.34
3 mo	204	6.86
4 mo	186	6.99
5 mo	183	6.56
6 mo	179	8.94
9 mo	166	6.63
12 mo	155	6.45

frequency of runs at the two week recording session (while the patient was still hospitalized) is consistent with the lower average PVC rates at this recording as previously reported (PR 12, A-3). Patients demonstrating runs at a given recording session tended to demonstrate runs at the following recording session. Thus, 19.2% (20/104) of tapes following a tape with a run contained a run, while 5.9% (68/1148) of tapes following a tape without a run showed a run.

For purposes of relating the presence of runs to various features observed during the acute phase of the index MI, 61 of 285 (21.4%) patients showing a run on one or more of the recording sessions two weeks to three months following their MI were defined as having early runs, and 48 out of 228 (21.1%) patients demonstrating one or more runs on the five recording sessions from four to twelve months post-MI, were defined as having late runs. The presence of early runs was strongly associated with the presence of late runs. Thus, 44% (23 out of 52 patients) with early runs and at least one tape in the late period had late runs, while only 14% (25 out of 174 patients) without early runs had late runs.

Clinical features observed during the acute phase of the MI were examined for their associations with the presence of early or late runs or both. Associations of particular interest are presented in Table II. In order to indicate the strengths of the associations, rather than just observe significance level, the odds ratio (O) has been computed. The presence of congestive heart failure, cardiomegaly, and left ventricular hypertrophy, along with ventricular or atrial arrhythmias and inter- and intra-ventricular conduction defects, all heralded an increased risk of runs in the ambulatory post-infarction period. Usually the degree of association was greater with the presence of runs during the early period.

In order to understand the relationship between the clinical features shown in Table II a multivariate logistic (D-18) was fit to the data predicting early runs. Table III presents the solution for nine variables chosen from those in Table II because of their contribution to the logistic equation. The standard error of estimate for each $\beta_i(\sigma_{\beta i})$ is from the matrix of second derivatives and is an asymptotic estimate. On the basis of the fitted equation the 285 patients with early tapes were ranked into quartiles of risk. The predicted percentage of patients with runs in each quartile and the actual observed percentage are given in Table IV, as is the observed rate of late runs for each group. The close fit of the model indicates that ambulatory patients at varying degrees of risk of runs of ventricular tachycardia can be identified from information observed during the acute phase of their index MI. The lack of independence also suggests that any analysis of ventricular tachycardia as a risk marker for subsequent sudden death should examine whether its presence adds to the risk which would be predicted solely on the basis of information obtainable during the index MI.

(1) J. P. Miller, "Codebook for Completing the Myocardial Infarction Patient Information Form," BCL Monograph No. 180, 1972.

Table II

Relationship Between Selected Clinical Features Observed During the Acute Phase of MI and Subsequent Ambulatory Ventricular Tachycardia

Clinical Feature	% of Total Population	Any Run %	Any Run O	Early Run %	Early Run O	Late Run %	Late Run O
Male	80	31	1.16	23	1.62	20	0.81
Over 60	40	34	1.37	27	1.64	23	1.16
Hx of MI	21	36	1.39	26	1.41	25	1.32
CHF	45	35	1.50	28*	2.03	26	1.61
CM	35	38*	1.77	32**	2.59	30*	2.08
LVH	14	46*	2.31	39**	2.83	26	1.37
CHF, CM & LVH	7	57*	3.46	43*	3.06	47*	3.67
Inferior MI	53	34	1.54	23	1.28	24	1.43
Posterior MI	5	7	0.16	0*	-	8	0.30
Transmural MI	77	31	1.22	22	1.33	20	0.86
PVC	92	31	2.89	22	2.89	22	5.22
VTACH	40	31	1.11	24	1.25	20	0.94
VFIB	5	53*	2.84	33	1.91	23	1.13
APC	35	34	1.34	28*	1.83	22	1.06
Conduction Defects	11	32	1.13	30	1.67	24	1.21
IVCD	20	39	1.63	34*	2.29	17	0.73
SGOT>240	30	41**	2.02	34**	2.66	28	1.70
CK>450	31	32	1.17	27	1.59	23	1.20
LDH>660	42	39**	2.07	32**	2.86	25	1.54
Overall	100	30	-	21	-	21	-

* p>.05; ** p>.01

Hx of MI - Prior history of documented MI; CHF - Congestive heart failure; CM - Radiographically determined cardiomegaly; LVH - Electrocardiographically observed left ventricular hypertrophy; PVC - Premature ventricular complex; VTACH - Runs of 3 or more PVCs; VFIB - Ventricular fibrillation; APC - Atrial premature complexes; Conduction Defects - First, second, or third degree atrioventricular conduction defects; IVCD - Any intraventricular conduction defect; SGOT - Peak daily SGOT concentration (mg/ml); CK - Peak daily CK concentration (mg/ml); LDH - Peak daily LDH concentrations (mg/ml).

Table III

Variable	Coefficient β_i*	β_i/σ_{β_i}
Male	-0.703	-1.62
Age	-0.024	-1.30
CM	-0.637	-1.88
LVH	-0.897	-2.20
Posterior MI	5.886	1.27
APC	-0.540	-1.68
Nonspecific IVCD	-0.661	-1.28
3^{o} Block	0.765	0.88
Log_{10} Peak LDH	-2.547	-3.66
α *	10.991	

* $P = \frac{1}{1 + \exp\ (\alpha + \beta X)}$ (see D-18)

Table IV

Observed Percent Risk of Early Runs in Quartiles of Risk from Logistic Solution

	Predicted Risk of Early Run (Range)	Observed Early Runs	Observed Late Runs
Q_1	4.97 (0.00-9.36)	2.78 (2/72)	13.33 (8/60)
Q_2	12.90 (9.43-16.13)	15.49 (11/71)	20.00 (12/60)
Q_3	22.48 (16.25-29.81)	23.94 (17/71)	20.34 (12/59)
Q_4	45.03 (29.92-79.38)	43.66 (31/71)	32.65 (16/49)

A-11. Evaluation of Arrhythmia Analysis Systems

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Support: RR 00396

We have been successful in establishing support for generating a standardized database for the evaluation of automated arrhythmia detectors (PR 12, A-17). This funding is in the form of a sole-source contract from the National Institutes of Health to the American Heart Association (AHA). The AHA ECG Committee will supervise contract operation and will subcontract the actual database implementation to Washington University. The database will consist of 160 three-hour two-channel digital tapes to be obtained primarily from Holter tapes. Other institutions which also routinely collect two-channel Holter tapes will be asked to submit tapes for possible inclusion in the database. The MECCA system (A-20), which is to be installed in the Jewish Hospital CCU, will be used to acquire rare and difficult to obtain arrhythmias, such as ventricular fibrillation and ventricular tachycardia. The 160-tape database will be divided into eight general arrhythmia classes (e.g., isolated PVCs, couplets, runs, bigeminy, ventricular tachycardia, ventricular fibrillation, etc.). Each class will consist of 20 tapes, half of which are intended for detector development use and half for detector evaluation. The last 1/2 hour of each three-hour tape will be annotated by three expert electrocardiographers. The preceding 2 1/2 hours is included for systems which require time to "learn" a given waveform. Database documentation will be provided in the form of database catalogues and microfilm records of the contents of each tape. Once established, the database is intended to be self-supporting, that is, users will be assessed sufficient charges to cover time and supplies needed to provide the user with requested materials.

Efforts to provide an abbreviated database of 19 one-hour annotated tapes (PR 12, A-17) have progressed slowly due to heavy demands on the time of annotating cardiologists and due to the desire to use the facilities of the Argus/2H system currently under development (A-2, A-3). This 19-hour database is intended to serve as a reference database until the completion of the national standard described above.

A-12. Evaluation of the Hewlett-Packard Arrhythmia Detector

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Support: RR 00396

A comparison has been made between the HP 78220 computerized arrhythmia detector and the Argus/H system (without edit) at the request of Hewlett-Packard. Although the HP 78220 was modeled after Argus, many additions and improvements have been included, particularly to reduce problems with false positive PVCs. This comparison used a 14-patient, 3.5-hour database, collected at Stanford University, which had already been processed by the HP 78220. Only 13 of the 14 tapes were used in this comparison due to the lack of cardiologist annotations for one patient. The analog tapes supplied by Hewlett-Packard were digitized and processed by the Argus/H system, using the original Argus CCU algorithms. The results were compared beat-by-beat with the HP 78220 results and with cardiologist annotations supplied by Stanford University. The results are as follows:

	Argus/H	HP 78220
PVC Detection	77.8%	81.6%
False-Positive PVCs	11.1%	1.6%

False-positive rates are given as a percentage of the number of PVCs. Only a moderate increase in PVC detection was seen; however, an 86% decrease in the false-positive rate was found. This is consistent with expected results based on knowledge of the extensive efforts of Hewlett-Packard and Stanford University to reduce false positives on the HP system.

A-13. Waveform Analysis and Evaluation Modeling

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Support: RR 00396

During the past year a generalized approach has been formulated for the problem of pattern recognition within single-valued time functions where context plays an important role. The recognition of arrhythmias in the ECG is such a problem. The proposed solution applies language-processing techniques developed recently in the field of computer science. These techniques, which are designed to be sensitive to contextual information, will be utilized within a higher-level ECG processing language to be developed as part of this project. The final analysis system will

consist of cascaded processors, each analyzing and extracting information from preceding stages. The data will take the form of character strings where each character has special meaning for the stage which generated it and for the succeeding stage. Each character will have an associated data vector to provide subsequent stages with quantitative information. For example, Aztec data can be considered to be a string of characters from the alphabet [f,s] where "f" represents flat segments and "s" slopes. Associated with each "f" and "s" would be a data vector specifying amplitude and duration. The goal of this approach is to evolve a more sophisticated arrhythmia analysis system with multi-channel and arrhythmia-diagnosis capabilities. The present Argus system is limited to the recognition of simple arrhythmias in a single ECG lead. In order to expand our understanding of pattern-detector evaluations, this project will include a mathematical analysis of evaluation design techniques. This analysis is intended to develop an evaluation model which can be used by the evaluator to relate database size and detector parameters. The model then will be tested on the proposed analysis system.

A-14. MECCA

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Support: RR 00396

Modifications and additional development of the MECCA system (PR 12, A-19) have been initiated in conjunction with efforts to develop a national standard database for arrhythmia detector evaluation (A-11). This CCU monitoring system provides a facility for capturing and digitizing two- to three-hour segments of ECG data containing transient and episodic arrhythmias. MECCA was originally designed to monitor one channel on each of 8 patients. The new configuration will allow 2-channel monitoring on each of 4 patients. The new system also will allow retrieval and display of any data saved on the system. Previously, the user could display only data currently being acquired. The ability to access any data on file will allow CCU personnel to review monitored patients' signals any time within the last 2 1/2 to 3 hours, thereby increasing the clinical utility of the system. The capture of an ECG data set was initiated in the past at the onset of a patient "code alarm" in the CCU. Since this usually resulted in loss of useful data which occurred after the alarm, a variable delay is being incorporated into the alarm algorithm. Hence, data subsequent to the alarm also can be captured. This modification is currently under development. The modification to allow retrieval of any system data is complete. The alarm-delay and the two-channel capability are scheduled to be completed this fall, at which time the system will be installed in the Jewish Hospital CCU for use in collecting ECG segments for the standardized database.

A-15. Feasibility Evaluation of the Esophageal-Lead ECGs

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Support: RR 00396
HL 18808

P-wave analysis plays a major role for the cardiologist in the understanding and diagnosis of arrhythmias. Although highly desirable, most arrhythmia detection systems do not employ P-wave analysis, due to the unreliability of current P-wave detection algorithms for a single ECG surface lead. As a result, most of these systems cannot accurately discriminate atrial from ventricular arrhythmias. The analysis of an additional surface lead is not likely to increase the reliability of P-wave detection since even diagnostic (12-lead) systems find detection of the P-wave troublesome. Recent work[1] has demonstrated that a small bipolar electrode suspended in the esophagus by a fine twisted pair of wires can provide reliable P-wave information with minimal patient discomfort, at least for short term recordings (a few hours). We are evaluating this electrode for use in long-term Holter recordings with the hope that, if satisfactory to the patient, the second Holter lead can be routinely replaced with an esophageal lead for recordings in the sudden death study (A-7). This lead combination (1 surface and 1 esophageal) can provide significantly more clinical information than two surface leads. Furthermore, the accuracy of computer analyses of this lead configuration would be greatly enhanced. The data obtained from such recordings are also excellent candidates for inclusion in the standard database for arrhythmia analyzer evaluation (A-12).

[1] J. M. Jenkins, D. Wu, and R. C. Arzbaecher, "Computer-Based Arrhythmia Classification Utilizing the PR Interval," Proceedings of the Conference on Computers in Cardiology, IEEE Catalog No. 76 CH 1160-1C, St. Louis, Missouri, pp. 149-156, October 7-9, 1976.

A-16. Mathematical Models for Estimation of Myocardial Infarct Size

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HL 17646

Plasma CK levels observed after myocardial infarction are determined by three processes: 1) release of enzyme from myocardium into blood,

2) distribution space of the released enzyme, 3) removal of CK from the vascular space or other pools. With the use of mathematical models we can better characterize these processes and more accurately estimate infarct size from plasma CK time-activity curves.

Recently we have continued our efforts to explain the disappearance of CK from plasma (PR 12, A-8). Previously we have shown that the plasma time-activity curves obtained after bolus injections of purified CK conform more closely to a double-exponential than to a single-exponential curve.[1] This finding suggests that CK distributes in extravascular pools as well as vascular, but does not account for the fact that the disappearance rate of plasma CK after myocardial infarction is only 21% as rapid in conscious dogs as the disappearance of plasma CK after bolus injections.

During the past year we have examined two factors which could explain the difference in the kinetics of the purified and native, circulating CK: 1) differences in the biochemistry of purified and endogenous CK activity, 2) continuing release of CK relatively late after infarction.

To explore the possibility that the purification process alters the enzyme, we used as injectates, extracts obtained from tissue by compressing the tissue with a muscle press. Extracts were obtained from both normal and ischemic tissue. In either case, the disappearance of the crude extract was not different from that of the purified enzyme in the same animal.[1] Thus, CK obtained from tissue, but not purified, appears to disappear at the same rate as purified CK.

Next we considered the possibility that native, circulating CK is biochemically different from CK obtained from myocardium. To examine this possibility we extracted plasma CK from dogs with high plasma CK levels as a result of induced myocardial infarction. The recipient dogs then received two bolus injections, one of purified CK and one of CK obtained from the plasma of donor dogs. In every case the disappearance of the CK extracted from plasma was much slower than that of the purified enzyme, but still faster than the rate of disappearance seen after myocardial infarction. Continuing release of the enzyme long after the peak of the plasma CK following myocardial infarction probably accounts for part of the observed differences in disappearance rates since the release of only a small amount of CK into the blood would markedly blunt the true disappearance.

The difference in the kinetics of the plasma and tissue enzyme implies that there are true biochemical differences in the two enzymes but, so far, we have not identified any differences. The two forms of CK are the same when compared by electrophoresis, radioimmunoassay, gel chromatography, and isoelectric focusing.

Characterization of the removal of CK from plasma enables us to compare the release function of CK into blood from the plasma CK time-activity curves obtained following myocardial infarction. Once we have defined the release function we can investigate the relationship of such variables as blood flow and region of infarction to the release function, thereby enabling us to more accurately define the relation of CK released to infarct size.[2-5]

(1) J. Markham, R. P. Karlsberg, R. Roberts, and B. E. Sobel, "Mathematical Characterization of Kinetics of Nature and Purified Creatine Kinase in Plasma," Proceedings of the Conference on Computers in Cardiology, IEEE Catalog No. 76 CH 1160-1C, St. Louis, Missouri, pp. 3-7, October 7-9, 1976.

(2) R. Roberts, R. P. Karlsberg, and B. E. Sobel, "Factors Retarding the Decline of Plasma CK Activity after Myocardial Infarction," American Journal of Cardiology, vol. 39, p. 317, 1977 (abstract).

(3) G. L. Clark, R. Roberts, and B. E. Sobel, "The Influence of Creatine Kinase (CK) Transport in Lymph on Plasma CK Curves after Myocardial Infarction," Clinical Research, vol. 25, p. 213A, 1977 (abstract).

(4) B. E. Sobel, "Biochemical Estimation of Infarction," presented at the International Symposium of the European Society of Cardiology, Vienna, June 1977 (abstract).

(5) B. E. Sobel, J. Markham, R. P. Karlsberg, and R. Roberts, "The Nature of Disappearance of Creatine Kinase from the Circulation and Its Influence on Enzymatic Estimation of Infarct Size," Circulation Research, in press.

A-17. External Evaluation of Regional Cardiac Lymph Flow in Intact Dogs

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Support: RR 00396
HL 07081
HL 17646

In recent studies we have shown that interruption of cardiac lymphatic efflux after coronary occlusion reduces the proportion of creatine kinase depleted from the heart, which appears in the blood.(1) Accordingly, characterization of cardiac lymph flow should permit refinement of enzymatic estimates of infarct size. In the present study, ^{99m}Tc-sulfur colloid, a potential tracer for imaging cardiac lymphatic structures, was injected into selected regions of the heart in 18 open chest and intact dogs. Serial gamma-camera images of the injection sites, regional lymphatics, and cardiac node were obtained for 24 hours prior to sacrificing the animals. Excised hearts and lymphatic structures then were scanned again and counted in vitro. In all five animals with tracer injected into the anterior wall of the left ventricle, radioactivity appeared in the cardiac node within two minutes. When accumulation of counts in the cardiac node in vivo was analyzed with curve-fitting techniques, 50% maximum and maximum values

occurred within 10 and 100 minutes respectively. In each of 2 dogs with occlusion of the cardiac lymphatics for 5 days prior to injection, appearance of radioactivity in the cardiac node was delayed markedly, with maximum values still not apparent after 200 minutes. Thus, qualitative evaluation of regional cardiac lymph flow from the anterior wall of the left ventricle can be assessed externally, potentially permitting refinement of enzymatic estimates of infarct size by incorporation of estimates of lymphatic efflux in individual experimental animals.[2]

[1] G. L. Clark, R. Roberts, and B. E. Sobel, "The Influence of Creatine Kinase (CK) Transport in Lymph on Plasma CK Curves after Myocardial Infarction," Clinical Research, vol. 25, no. 3, p. 213A, April 1977 (abstract).

[2] G. L. Clark, B. A. Siegel, and B. E. Sobel, "Qualitative External Evaluation of Regional Cardiac Lymph Flow in Intact Dogs," The Physiologist, in press (abstract).

A-18. Modification of Infarct Size

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Support: HL 17646

Studies were performed in the Cardiac Care Unit at Barnes Hospital to assess the effect of selected pharmacological agents on infarct size, ventricular dysrhythmia, and hemodynamics in patients with myocardial infarction. Infarct size was estimated from serial plasma creatine kinase (CK) changes during a 72-hour interval. Infarct size was predicted from CK values projected by least squares approximation to the log normal curve best fitting data obtained hourly for 7 hours after the initial plasma CK elevation. The difference between predicted (ISP) and observed infarct sizes was compared to that of controls who were matched for predicted infarct size. All Holter tapes were digitized and processed by the Argus/H computer system. Hemodynamics, including cardiac output, were determined by the Swan-Ganz thermodilution technique and the effect of the drug assessed by comparing hemodynamics before and after administration.

Studies initiated in 1975, to evaluate the effects of acebutolol in patients with myocardial infarction, were completed in 50 patients with acute myocardial infarction. Acebutolol (10-50 mg every four hours) was administered intravenously to 25 patients for 24 hours and results were compared to 25 concomitant controls who did not receive acebutolol. Acebutolol is a cardioselective beta blocker which has marked chronotropic effects with minimal ion-tropic effects. Patients were excluded from the study if the pulmonary wedge pressure was greater than 16 mm Hg, the arterial systolic pressure was less than 110 mm Hg, or the heart rate was less than 70 beats/minute. The objective was to maintain the heart rate near 70 beats/minute with a wedge pressure below 18 mm Hg and cardiac output greater than 4.0 liters/minute. Despite the high doses of acebutolol, patients tolerated the drug well. In only three patients was the drug discontinued, in two because of the development of AV block and in another for hypotension and bradycardia. The hypotension was only transient, lasting for about 20 minutes.

Acebutolol did not significantly change the wedge pressure, peripheral resistance, or systemic pressure. Cardiac output decreased from 5.1 1/minute $\pm$.2 to 4.4$\pm$2($p<.05$), heart rate decreased from 82$\pm$2/minute(S.E.) to 71$\pm$3($p<.05$), and hourly PVC rate decreased by 60% compared to controls ($p<.05$). These favorable effects occurred without changing overall infarct size (88$\pm$13 CK-g-eq) compared to controls (71$\pm$13). Thus, acebutolol decreased heart rate and ventricular dysrhythmia without elevating wedge pressure or increasing enzymatically estimated infarct size in patients with evolving myocardial infarction.

The study, initiated in 1976 to assess the effect of dobutamine in patients with acute myocardial infarction, has been completed in 50 patients. Dobutamine is a beta-antagonist which increases myocardial contractility without significantly increasing heart rate or blood pressure. It may increase coronary flow by coronary vasodilation. Dobutamine was administered IV (1 - 40 mcg/kg/min) to patients with moderate to severe hemodynamic impairment, as evidenced by a wedge pressure of >15 mm Hg and cardiac index of <2.5 liters/m^2/BSA. Dobutamine was given to 25 patients after prediction of infarct size and results compared to 25 control patients matched for ISP. Results showed marked improvement in cardiac output, with decreased pulmonary-wedge pressure and no changes in heart rate, blood pressure, or rhythm. More importantly, these results were not associated with an apparent increase in infarct size, in marked contrast to the results with isoproteronol or norepinephrine in which hemodynamic improvement is at the expense of an increase in infarct size. The hemodynamic effects of dobutamine occur immediately. Since the drug's half life in plasma is only 3 minutes its effect can be terminated promptly. Thus, the results obtained indicate that dobutamine has several advantages compared to other agents with positive inotropic effects in the treatment of cardiac failure in patients with acute myocardial infarction.

Studies initiated to assess the effect of nifedipine have been completed. Nifedipine, a calcium antagonist, is a potent dilator of smooth muscle and is known to increase coronary flow and decrease systemic resistance, both of which may protect ischemic myocardium. Studies were performed

in 17 treated patients and 17 controls. Nifedipine was associated with a decrease in pulmonary-wedge pressure, peripheral resistance, and mean blood pressure, but with an increase in cardiac output. It had no apparent effects on infarct size or arrhythmias. Since it is a calcium antagonist it would be expected to block the slow, secondary, calcium dependent current and decrease some ventricular arrhythmias. The lack of effect on arrhythmias suggests that slow current may not be a prominent mechanism in this clinical setting.

Studies are now in progress to assess the effect of aprindine in patients with acute myocardial infarction. Aprindine is an antiarrhythmic agent with quinidine-like properties but a half-life of 12-16 hours. Preliminary results in 10 patients show aprindine to be effective in the treatment of ventricular arrhythmias without any apparent deleterious effect on hemodynamics or infarct size.

(1) P. D. Henry, R. Shuchleib, E. Weiss, E. Hoffman, R. Roberts, and B. E. Sobel, "Protection of Ischemic Myocardium in Conscious Dogs with Nifedipine," American Journal of Cardiology, vol. 37, p. 142, 1976.

(2) A. L. Gutovitz, B. Cole, P. D. Henry, B. E. Sobel, and R. Roberts, "Resistance of Ventricular Dysrhythmia to Nifedipine, a Calcium Antagonist," to be presented at the American Heart Association, Miami Beach, Florida, November 1977; Circulation, in press (abstract).

(3) K. S. Gowda, T. A. Gillespie, H. D., Ambos, B. E. Sobel, and R. Roberts, Effects of External Counterpulsation on Enzymatically Estimated Infarct Size and Ventricular Dysrhythmia," British Heart Journal, in press.

(4) T. A. Gillespie, H. D. Ambos, B. E. Sobel, and R. Roberts, "Effects of Dobutamine in Patients with Acute Myocardial Infarction," American Journal of Cardiology, vol. 39, pp. 588-594, 1977.

(5) T. A. Gillespie, R. Roberts, H. D. Ambos, and B. E. Sobel, "Salutary Effects of Dobutamine on Hemodynamics without Exacerbation of Arrhythmia or Myocardial Injury," Circulation, supplement II, vol. 51 and 52, p. 76, 1975 (abstract).

(6) R. P. Karlsberg, P. D. Henry, S. A. Ahmed, B. E. Sobel, and R. Roberts, "Lack of Protection of Ischemic Myocardium by Verapamil in Conscious Dogs," European Journal of Pharmacology, vol. 42, pp. 339-346, 1977.

(7) R. P. Karlsberg, B. E. Sobel, and R. Roberts, "Appraisal of a Calcium Antagonist (Verapamil) on Infarct Size and Coronary Flow," Clinical Research, vol. 24, p. 519A, 1976 (abstract).

(8) H. D. Ambos, R. Roberts, G. C. Oliver, J. R. Cox, Jr., and B. E. Sobel, "Infarct Size: A Determinant of Persistence of Severe Ventricular Dysrhythmia," American Journal of Cardiology, vol. 37, p. 116, 1976 (abstract).

(9) E. J. Hoffman, E. S. Weiss, R. Roberts, B. E. Sobel, and P. D. Henry, "Protection of Ischemic Myocardium in Conscious Dogs Treated with Nifedipine," Circulation, supplement II, vol. 51 and 52, p. 196, 1976 (abstract).

(10) H. D. Ambos, R. Roberts, C. W. Loh, and B. E. Sobel, "Late Ectopic Ventricular Beats: Precipitants of Repetitive Dysrhythmia," Circulation, supplement II, vol. 54, p. 8, 1976 (abstract).

(11) E. M. Geltman, S. M. Nordlicht, J. S. Gwinn, Jr., H. D. Ambos, and R. Roberts, "Effects of Aprindine in Patients with Acute Myocardial Infarction," to be presented at the American Heart Association, Miami Beach, Florida, November 1977; Circulation, in press (abstract).

A-19. Ischemic Heart Disease SCOR Computer System

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Support: RR 00396
HL 17646

The SCOR Interdata computer system (PR 12, A-12) has been expanded to include a magnetic tape cassette, a scan converter for video displays, and a multiprobe interface/controller for collection of radioisotope data. The standard Interdata cassette unit features a dual transport, 1,000 byte/sec read/write speed, and read-after-write check. The unit accomodates 0.5-Mbyte cassettes which can provide storage for processed data on a per-patient basis.

An upgraded version of a previously implemented Ramtek GX-100A graphic display system (PR 10, B-9) has been added to provide single frame grey- and color-scale images for viewing on a Conrac video monitor. The solid-state memory of the unit is organized into an array of 256 lines and 256 pixels/line where each pixel is represented by 8 bits, thereby yielding 256 levels of grey. In addition, a programmable video look-up table provides "on-the-fly" grey-to-color-scale mapping. The color scale may be organized as desired, using any combination of the three additive primary colors for up to 256 colors. The monitor offers push-button selectivity between the grey or color-scale inputs.

Previously implemented software has been modified and augmented to support the upgraded unit. The problem of grey-to-color-scale mapping has been approached by adopting the internationally accepted Commission Internationale de l'Eclairage (C.I.E.) chromaticity diagram as reference. Any given level of grey may then be mapped to any desired color by arbitrarily

assigning x, y, and z coordinates to the grey levels and making use of the following relation,

$$[r\ g\ b] = [x\ y\ z]\ [A]^{-1}.$$

In this equation, the vector [x y z], whose components are known as chromaticity coordinates, is obtained from the C.I.E. chromaticity diagram and [A] is a matrix obtained from the monitor manufacturer's specifications. The resulting vector [r g b] yields the chromatic coefficients with respect to the primary color drives, red, green, and blue, of the monitor.

Photographic hard copy of the video display has been provided by a camera system consisting of a Nikon F body equipped with a 55 mm f/3.5 Micro Nikor lens and a Speed Magnoy polaroid pack. The versatility of the camera system is demonstrated in its ability to produce black and white or color pictures on either polaroid or 35 mm formats.

A modified version of a previously developed multiprobe system (PR 9, C-15) has been installed for the purpose of collection and analysis of radioisotope data from a remote experimental site in the cardiovascular research laboratories. Cables have been installed between the remote site and the Interdata main frame to provide console operation of the computer, footswitch initialization of collection, and transmission of the serialized data from two scintillation detectors. Analysis of the data includes correction for isotope decay and background subtraction, in addition to sorting, printing, and plotting the time-activity curves.

The SCOR data system has been used in several clinical studies completed during the past year.[1-8]

(1) B. E. Sobel, "The Importance of Electrophysiological, Enzymatic, and Tomographic Estimation of Infarct Size," in Cardiovascular Nuclear Medicine, Second Edition, C. V. Mosby Company, St. Louis, in press.

(2) K. S. Gowda, T. A. Gillespie, H. D. Ambos, B. E. Sobel, and R. Roberts, "Effects of External Counterpulsation on Enzymatically Estimated Infarct Size and Ventricular Dysrhythmia," British Heart Journal, in press.

(3) P. B. Corr, and B. E. Sobel, "Automated Data Processing. An Essential Decision-Making Aid in the Treatment of Acute Myocardial Infarction," in Advances in Cardiology, vol. 20, J.H.K. Vogel, ed., S. Karger, Basel, Switzerland, pp. 54-71, 1977.

(4) R. Roberts, V. deMello, and B. E. Sobel, "Deleterious Effects of Methylprednisolone in Patients with Myocardial Infarction," Circulation, vol. 53, supplement I, pp. I-204-I-206, 1976.

(5) T. A. Gillespie, H. D. Ambos, B. E. Sobel, and R. Roberts, "Effects of Dobutamine in Patients with Acute Myocardial Infarction," American Journal of Cardiology, vol. 39, pp. 588-594, 1977.

(6) E. S. Weiss, S. A. Ahmed, M. J. Welch, J. R. Williamson, M. M. Ter-Pogossian, and B. E. Sobel, "Quantification of Infarction in Cross Sections of Canine Myocardium in Vivo with Positron Emission Transaxial Tomography and ^{11}C-Palmitate," Circulation, vol. 55, pp. 66-73, 1977.

(7) B. E. Sobel, J. Markham, and R. Roberts," Factors Influencing Enzymatic Estimates of Infarct Size," American Journal of Cardiology, vol. 39, pp. 130-132, 1977.

(8) B. E. Sobel, E. S. Weiss, M. J. Welch, B. A. Siegel, and M. M. Ter-Pogossian, "Detection of Remote Myocardial Infarction in Patients with Positron Emission Transaxial Tomography and Intravenous ^{11}C-Palmitate," Circulation, vol. 55, pp. 853-857, 1977.

A-20. Electrophysiological and Biochemical Factors Underlying the Genesis Dysrhythmias Due to Myocardial Ischemia

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Support: HL 17646
Missouri Heart Grant-in-Aid

During the past year, techniques have been developed to record simultaneous epi-, endo-, and mid-myocardial bipolar electrograms from normal and ischemic regions of the left ventricular wall in a feline preparation exhibiting reproducible ventricular dysrhythmia early after coronary occlusion.[1-3] An automated analysis of the waveforms in real time with a PDP-12 computer system was developed to permit pulse by pulse determination of the minimum and maximum amplitudes, rise time, pulse width, and dV/dt prior to and at selected intervals after coronary occlusion.[1] Myocardial ischemia results in a progressive and significant increase in pulse width and rise time and a decrease in dV/dt in waveforms obtained from ischemic regions. Normal regions showed no significant alterations during ischemia. Ventricular dysrhythmia ensued when pulse alterations became maximal (i.e. 2.3±0.3 minutes after occlusion) and partial, but significant, regression of these pulse abnormalities occurred in epicardial and myocardial areas prior to the termination of the dysrhythmia. Thus, malignant ventricular dysrhythmias secondary to myocardial ischemia are characterized by slowed conduction and asynchronous depolarization within ischemic sites of the

left ventricle. The computerized analysis system permits pulse-by-pulse analysis of electrophysiological factors underlying ventricular premature beats and/or ventricular fibrillation during ischemia, as well as the influence of various interventions on these dysrhythmias.

Subsequently, this system was utilized to determine whether distinct electrophysiological differences underlie dysrhythmias due to coronary occlusion versus those due to coronary reperfusion. In the cat, proximal left anterior descending (LAD) coronary occlusion resulted in a reproducible ventricular dysrhythmia ending at 33.5±1.5 minutes. Reperfusion at 35 minutes after occlusion also resulted in a severe ventricular dysrhythmia. Electrophysiological differences between these two dysrhythmias include: (1) slowed conduction, manifested by decreased dV/dt (39±13% (SE) of control), preceded occlusion dysrhythmia with return toward normal (76±5% of control) with reperfusion dysrhythmia, (2) conduction time in ischemic zones was delayed ($p<.01$) with dysrhythmia due to occlusion but not reperfusion, (3) asynchronous depolarization (pulse width = 606±13% of control) preceded occlusion but not reperfusion dysrhythmia (131±17% of control), (4) the idioventricular escape rate with intense vagal stimulation was 62±6 beats/minute, which was similar to control levels with occlusion dysrhythmia but increased ($p<.01$) with reperfusion dysrhythmia (188±12 beats/minute), and (5) reperfusion dysrhythmia was suppressed by atrial pacing but the occlusion dysrhythmia was exacerbated. Thus, it appears that two distinct mechanisms may underlie these two rhythm disturbances, most probably reentry in the case of occlusion dysrhythmia, whereas enhanced ventricular automaticity may underlie reperfusion dysrhythmia. Since both may be potentially important in the sudden death syndrome in man, each may require different therapeutic interventions.

Concurrent with these studies we determined whether or not regional adrenergic activity contributed to malignant dysrhythmia early after ischemia.[3,5,6] Regional adrenergic activity was measured by radioimmunoassay of myocardial cyclic AMP in 66 pairs of fast frozen biopsies from ischemic and normal zones of the left ventricle, obtained simultaneously at selected intervals after coronary occlusion. Computer programs written for the PDP-12 system subtract the mean blank count for each tube, plot the standard curve and obtain the best-fit linear equation, and calculate the cyclic nucleotide concentration in each sample tube on the basis of percent binding with results expressed as picomoles/mg protein of cyclic AMP. Initial studies revealed that cyclic AMP increased progressively in ischemic, but not in normal zones, reaching twofold increases at 15 minutes after occlusion and returning to control levels at termination of the dysrhythmia. Peak increases in cyclic AMP at 15 minutes preceded the peak PVC frequency at 15 - 20 minutes. In cats who developed VF, compared to those with PVCs only, cyclic AMP increased markedly 2.5 minutes after occlusion (10.6±.8, $n=13$) compared to (6.9±.6, $n=6$, $p<.01$). Pretreatment with propranolol prevented any increase in cyclic AMP (confirming that adrenergic activity was responsible) and reduced PVCs during the first 15 minutes from 665±63 to 348±129. Electrical induction of PVCs or VF did not increase cyclic AMP in normal or ischemic hearts, indicating that ventricular fibrillation early after ischemia may be promoted by increased regional adrenergic activity in ischemic myocardium.

Currently studies are underway, using efferent sympathetic and parasympathetic cardiac nerve recording techniques. These neural waveforms will be analyzed by the computer system, using high-speed Fourier transformations to allow filtering in the frequency domain with subsequent D/A conversion of the reconstituted waveforms for physiological nerve stimulation. This technique will allow a more physiological assessment of neural inputs to the heart than current supramaximal stimulation techniques. The system will allow an assessment of the role of neural stimulation on the electrophysiological alterations occurring with ischemia, as well as the amount of cyclic nucleotide produced for a given neural input. Computer techniques are currently being developed to analyze intracellular action potentials obtained from isolated canine Purkinje fibers and papillary muscles. These techniques will be utilized to determine the influence of alterations in membrane lipids on ionic conductances with extrapolation and/or correlation to ischemic conditions.

(1) F. X. Witkowski, B. E. Sobel, and P. B. Corr, "Characterization of Regional Myocardial Electrograms with an Automated System for Pulse Analysis," Proceedings of the Conference of Computers in Cardiology, IEEE Catalog No. 76 CH 1160-1C, St. Louis, Missouri, pp. 19-28, October 7-9, 1976.

(2) P. B. Corr, F. X. Witkowski, and B. E. Sobel, "Mechanisms Contributing to Malignant Dysrhythmias Induced by Ischemia," Journal of Clinical Investigation, in press, pending revision.

(3) P. B. Corr, F. X. Witkowski, and B. E. Sobel, "Increased Regional Cyclic AMP and Sympathetic Tone Underlying Ventricular Fibrillation Induced by Ischemia," presented at the Sixteenth Annual Meeting of the Association of University Cardiologists, Inc., Phoenix, January 1977 (abstract).

(4) P. B. Corr, F. X. Witkowski, and B. E. Sobel, "Increased Adrenergic Tone in Ischemic Myocardium Underlying Ventricular Fibrillation," Clinical Research, vol. 25, p. 454A, 1977 (abstract).

(5) P. B. Corr, and B. E. Sobel, "Mechanisms Contributing to Dysrhythmias Induced by Ischemia and Their Therapeutic Implications," in Advances in Cardiology, vol. 22, J.H.K. Vogel, ed., S. Karger, Basel, Switzerland, in press.

A-21. Ultrasound Cardiac Imaging, Digisonics System

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Support: RR 00396
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Instrumentation for two-dimensional, cross-sectional ultrasonic imaging of the heart has been purchased from Digisonics, Inc. The DIGISCAN (R) system consists of a sector arm containing a fixed transducer which is synchronized with a data collection system for M-mode recording onto magnetic tape. In this fashion, M-mode data from a sector scan of the heart are obtained and subsequently processed off-line by computer. The ultrasonic scan is performed along a fixed axis (either transverse or longitudinal), and the data stored on magnetic tape are referenced according to time and the position of the transducer along the proscribed axis. Off-line computer analysis of the recorded M-mode data is accomplished by programs obtained from Digisonics and modified for the SCOR Interdata computer. The data are then displayed as 24 cross-sectional images, representing an averaged cardiac cycle, on a television monitor connected to the Ramtek display system (A-19). Thus, an archetypical systole-diastole is viewed as 24 sequential, time-spaced frames which may be recorded on tape for video review or photographed in stop-frame to facilitate measurements of cardiac dimensions.

Preliminary studies have provided an opportunity to validate computer programs for the DIGISCAN system, to test various transducers, and to define limitations of imaging capability due to the restriction of tracking the transducer along a single axis. In these studies myocardial wall motion, intracardiac dimensions, and valvular excursions have been delineated.

Additional studies are planned for comparison of estimates of left heart dimension, as obtained by the DIGISCAN system, with both angiographic and radionuclide estimates of ventricular dimensions and myocardial function (PR 12, A-13). Other studies will examine ventricular wall motion dysfunction in subjects who have had myocardial infarction, with results to be compared with radionuclide imaging of wall motion abnormalities.[1-4]

(1) J. W. Mimbs, D. E. Yuhas, J. G. Miller, A. N. Weiss, and B. E. Sobel, "Detection of Myocardial Infarction in Vitro Based on Altered Attenuation of Ultrasound," Circulation Research, in press.

(2) M. O'Donnell, J. W. Mimbs, B. E. Sobel, and J. G. Miller, "Ultrasonic Attenuation in Normal and Ischemic Myocardium," in Proceedings of the Second International Symposium on Ultrasonic Tissue Characterization, Bethesda, Maryland, June 1977, in press.

(3)M. O'Donnell, J. W. Mimbs, B. E. Sobel, and J. G. Miller, "Ultrasonic Attenuation of Myocardial Tissue: Dependence on Time after Excision and on Temperature," Journal of the Acoustical Society, in press.

(4)P. A. Ludbrook, J. D. Byrne, P. B. Kurnik, and R. C. McKnight, "Influence of Reduction of Preload and Afterload by Nitroglycerin on Left Ventricular Diastolic Pressure-Volume Relations and Relaxation in Man," Circulation, in press.

A-22. Real-Time Digital Echocardiography

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Support: RR 00396
HL 18144

Instrumentation for the acquisition and digital processing of ultrasonic echoes has been implemented (PR 12, A-22). It is based on burst-analog-sampling circuitry coupled to two Motorola 6800 microprocessors operating in parallel. Analog samples acquired at a high rate are stored in a series of sample-and-hold circuits. During the period between ultrasonic pulses, samples are accessed slowly for analog-to-digital conversion.(1)

One microprocessor controls real-time operation and can dynamically adjust analog gain, which gives the capability for automatic depth compensation. It collects 256 samples from each echo. These samples are analyzed in real-time by the second processor for data reduction and storage in a large random-access memory (12K). This buffer typically contains a 10 cm by 4 sec echo history. The system generates either A-mode or M-mode displays in real-time or frozen images from the large buffer. The ability to capture a significant M-mode record in digital form offers the opportunity to perform a variety of on-line image enhancing steps.

Present efforts are directed at improving the convenience of operator interaction with the ECHO system with, for example, the keyboard entry of all control functions and software production of distance and time markers and alphanumerics in the displays. Under development are algorithms for automatically compensating for loss of signal amplitude as a function of tissue depth and for real-time data reduction of the echo signal.

(1)R. J. Myrick and R. M. Arthur, "Real-Time Digital Echocardiography Using Burst Analog Sampling," IEEE Transactions on Sonics and Ultrasonics, vol. SU-24, pp. 19-23, 1977.

A-23. Interactive Digital Acquisition of Electrocardiograms

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Support: RR 00396
HL 18144
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A digital ECG cart has been designed and implemented to test signal quality of 6-second segments of three simultaneous leads acquired at 500 samples/second (PR 12, A-21).[1] The tests were devised to eliminate records which might not meet the demands of automatic ECG analysis systems and included checks for signal out-of-range, transient content, presence of a QRS complex, baseline-shift, and no noise content.

Upgrading of this ECG preprocessor (originally built around the Intel 8008 microprocessor) by incorporation of an Intel 8080A CPU and a serial port has been completed. Programs have been restructured and a number of displays added, including verification of calibration pulse capture, a running display during acquisition, and indication of R-wave detection.

The histograms used to determine baseline shift and noise content are also shown. The operator is informed via the CRT display which test, if any, was failed. We are now studying an 800-record pediatric ECG database on FM analog tape to determine both the distribution of signal-quality problems encountered in six-second segments and the number of segments which must be tested in order to find an error-free signal in a given record.

Pre-processor performance is assessed with the aid of a TI-980B minicomputer and a digital plotter. All signal quality problems are listed, along with the baseline value, baseline shift, and RMS voltage at frequencies above 40 Hz for each lead during each RR interval. ECG waveforms with superimposed baselines and the histograms used to determine baselines and noise content are plotted.

[1] R. M. Arthur, D. G. Wantzelious, A. Hernandez, and A. N. Weiss, "Interactive Acquisition of Diagnostic Electrocardiograms," Proceedings of the Conference on Computers in Cardiology, IEEE Catalog No. 76 CH 1160-1C, St. Louis, Missouri, pp. 307-311, October 7-9, 1976.

A-24. Computers in Cardiology

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Support: RR 00396
National Institutes of Health

The 1976 international meeting of the Computers in Cardiology Conference was held in St. Louis, October 7-9, at the Chase Park-Plaza Hotel. All local arrangements were made by BCL personnel. The meeting was attended by approximately 250 people, 15% of whom were from other countries. Travel support was provided by the NIH for session chairmen and European authors. The conference consisted of three main sessions and nine workshops with a total of 71 presentations. Subsequent to the meeting, papers from each author were edited and compiled into a proceedings which has been published by the IEEE. After the 1976 meeting the American Heart Association (AHA) expressed an interest in sponsoring our yearly conference. An informal proposal to this effect was submitted to the AHA and approved. This sponsorship includes American Medical Association continuing education credit for U. S. physicians. The 1977 conference will be held in Rotterdam, the Netherlands, at Erasmus University, September 29 - October 1. We are assisting the Rotterdam group in the preparations for this meeting and the NIH is again providing international travel support.

B. Tomography Systems

Stimulated by the clinical impact of the EMI transmission tomographic scanner in 1973 experimental studies were initiated in collaboration with the Division of Radiation Sciences to evaluate positron coincidence-detection as a method for emission reconstruction tomography. This collaborative activity resulted in a prototype scanner called PETT (Positron-Emission Transaxial Tomograph). A series of modifications following preliminary studies led to the development of a clinically usable scanner called PETT III. This development was facilitated by the application of specialized digital technology for coincidence detection and scanner control. A back-projection algorithm, based on a convolution approach, was implemented in a minicomputer to effect reconstructions of radioisotope activity from coincidence detections.

Extensive studies in patients and animals have been conducted with the PETT III scanner in collaboration with the Division of Neurology and Cardiology. A new scanner, called PETT IV, is nearing completion. This new scanner utilizes concepts developed with its predecessor, PETT III, but incorporates a novel technique for the simultaneous collection of four tomographic slices from a single set of detectors so that the total scan time is reduced substantially. The multiple-slice scanner is to be used by the SCOR project for the quantification of regions of myocardial ischemia and infarction *in vivo* in experimental animals and in patients.

Although ultrasound has proven to be a useful source of diagnostic information, results of examinations based on current ultrasonic methods are primarily qualitative and pictorial. In contrast, the development of ultrasonic computerized tomography offers promise of providing quantitative information in addition to a picture. Each matrix element of the reconstructed image contains the local value of the ultrasonic parameter of interest. This should allow the investigator to make measurements of a far more localized nature than is now possible without structural damage to the tissue, making possible the use of ultrasound for detailed characterization of tissue. The feasibility of ultrasonic reconstructive tomography has been demonstrated using either attenuation or phase velocity as the ultrasonic index.

A collaborative effort with the Physics Department has been undertaken to develop ultrasonic computerized tomography into a clinically useful tool. Research in at least two areas is needed. First, methods for ultrasonic computerized tomography itself must be improved. Progress during the last year on this issue is reported below. Second, the results of quantitative ultrasonic measurements must be correlated with independent indices of tissue pathology so that the results of an ultrasonic computerized tomography image can be meaningfully interpreted. Research on the use of ultrasound for quantitative tissue characterization is proceeding rapidly in a number of institutions, including our own. Thus, we anticipate that information relating quantitative ultrasonic indices to tissue pathology will be available for use in conjunction with ultrasonic computerized tomography.

B-1. Ultrasonic Tomography: Applications

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Support: RR 00396
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Ultrasonic characterization of tissue pathology is a rapidly developing field of research with significant progress in many areas.[1,2] In any method based on ultrasound two independent ultrasonic parameters can be measured. Typically, one measures the propagation time, which yields information about the ultrasonic velocity, and the amplitude of the received signal, which yields information about the ultrasonic attenuation. Greenleaf[3,4] demonstrated that both of these parameters can be measured locally by using tomographic reconstruction methods, although methodological difficulties limited the accuracy of these early reconstructions. More recent results by the Mayo group[5] and Glover[6] have shown that the time of flight method is capable of producing good reconstructions.

Our current efforts have been focused on methods for reconstructions based on ultrasonic attenuation. Although the methodological difficulties encountered in making accurate attenuation measurements are more severe than those encountered in time of flight measurements, ultrasonic attenuation has been demonstrated to be a meaningful indicator of tissue pathology.[1,2] For example, Figure 1 summarizes the results of our ultrasonic tissue characterization studies, making use of an index based on attenuation to differentiate normal and ischemically injured myocardium.[7] In Section B-2 theoretical considerations applying to ultrasonic attenuation tomography are discussed. The description of our prototype scanner and results of phantom studies in-vitro animal experiments are given in Section B-3.

[1] Proceedings of First International Symposium on Ultrasonic Tissue Characterization, National Bureau of Standards, Publication No. 453, 1976.

[2] Proceedings of Second International Symposium on Ultrasonic Tissue Characterization, National Bureau of Standards, 1977, in press.

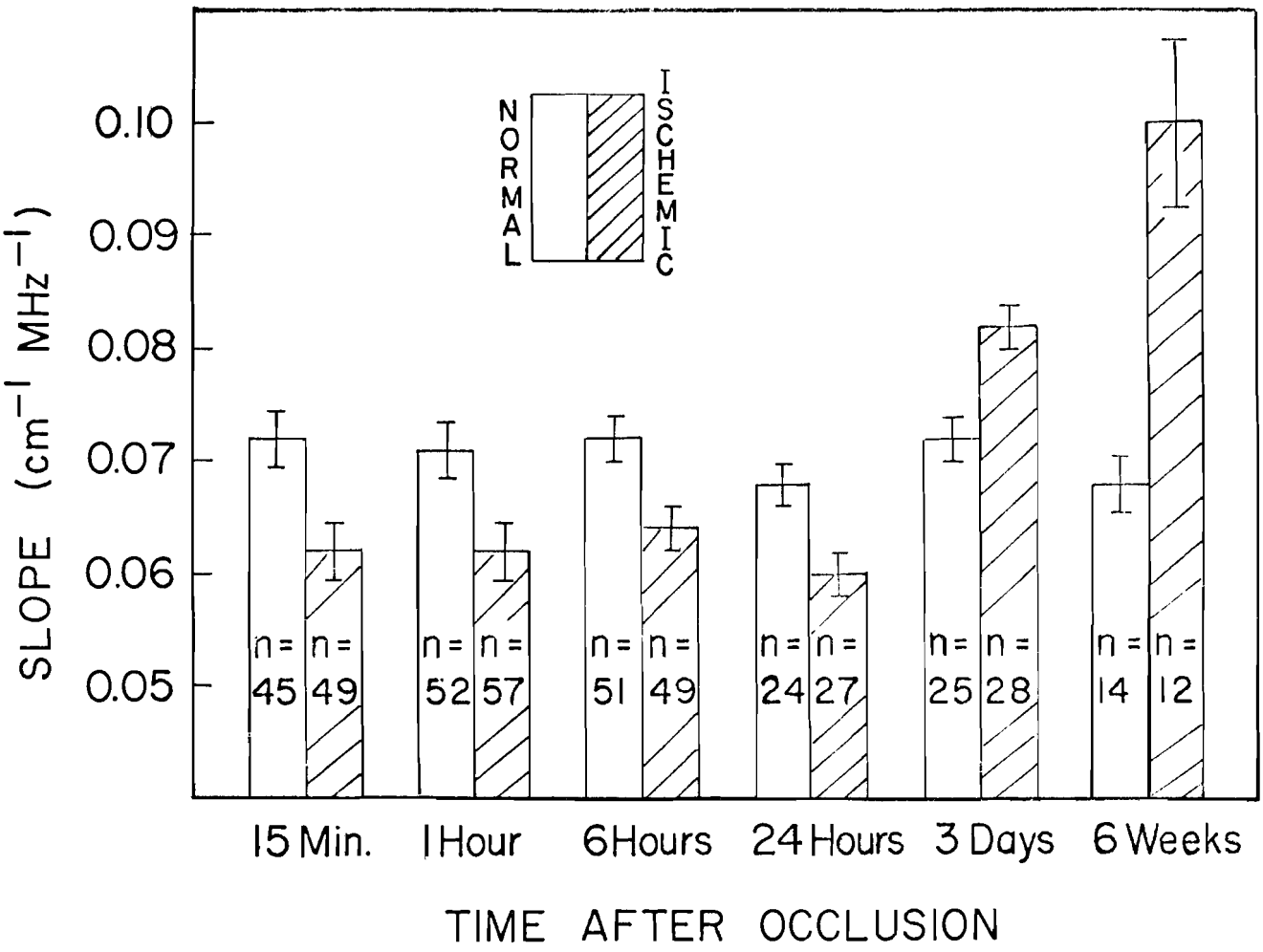

FIGURE 1.

SLOPE OF ULTRASONIC ATTENUATION VS. FREQUENCY FOR NORMAL AND ISCHEMICALLY INJURED DOG MYOCARDIUM MEASURED IN VITRO ON EXCISED TISSUE. ISCHEMIC INJURY WAS INDUCED BY OCCLUSION OF THE LEFT ANTERIOR DESCENDING CORONARY ARTERY.

(3) J. F. Greenleaf, S. A. Johnson, S. L. Lee, G. T. Herman, and E. H. Wood, "Algebraic Reconstruction of Spatial Distributions of Acoustic Absorption Within Tissue from Their Two-Dimensional Acoustic Projections," in Acoustic Holography, vol. 5, P. S. Green, ed., Plenum Press, New York, 1974.

(4) J. F. Greenleaf, S. A. Johnson, W. F. Samayo, and F. A. Duck, "Algebraic Reconstruction of Spatial Distributions of Acoustic Velocities in Tissue from Their Time-Of Flight Profiles," in Acoustic Holography, vol. 6, N. Booth, ed., Plenum Press, New York, 1975.

(5) R. Balasubramanian, J. F. Greenleaf, P. J. Thomas, and S. A. Johnson, "Temperature Coefficients of Acoustic Speed in Various Human Tissues," in Proceedings of 2nd International Symposium on Ultrasonic Tissue Characterization, National Bureau of Standards, 1977, in press.

(6) G. H. Glover, and J. C. Sharp, "Reconstruction of Ultrasound Propagation Speed Distributions in Soft Tissue: Time of Flight Tomography," IEEE Transactions on Sonics and Ultrasonics, vol. SU-24, no. 4, July 1977.

(7) M. O'Donnell, J. W. Mimbs, B. E. Sobel, and J. G. Miller, "Ultrasonic Attenuation in Normal and Ischemic Myocardium," in Proceedings of 2nd International Symposium on Ultrasonic Tissue Characterization, National Bureau of Standards, 1977, in press.

B-2. Ultrasonic Tomography - Theoretical Considerations

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Support: RR 00396
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Ultrasonic-attenuation tomography is compromised by several effects that cause the actual propagation of ultrasound to differ significantly from the ideal propagation that would meet the assumptions for tomographic reconstruction. Reflection losses, phase cancellation at piezoelectric receivers, refraction, and finite beam width are potentially severe problems. For certain tissues an additional problem may occur due to anisotropy of the ultrasonic-attenuation coefficient with respect to fiber orientation.

Reflection Losses

Partial reflection and transmission of ultrasound will occur whenever an ultrasonic wave is incident upon a boundary between two media of differing acoustic impedance. The propagation of ultrasound through tissue may be modeled as a ray of ultrasound propagating through layers of media (Figure 1). If there are N layers between the transmitter and receiver there are N-1 transmission coefficients T_i at the boundaries between layers. The ultrasonic pressure amplitude detected at the receiver is

$$P(\omega) = P_0(\omega) \exp[-\int_0^D \alpha(\omega,z)dz] \prod_{i=1}^{N-1} T_i(\theta) \qquad (1)$$

where P_0 is the initial pressure generated at the transmitter, D is the distance between transmitter and receiver, ω is the ultrasonic frequency, and α is the attenuation coefficient as a function of position along the ray. The attenuation is a piece-wise continuous function of z. Field pattern variations along the ray have been neglected since they are normalized out by comparing the measurements in tissue to those in which only a water path exists between transmitter and receiver. Taking the logarithm of (1) yields

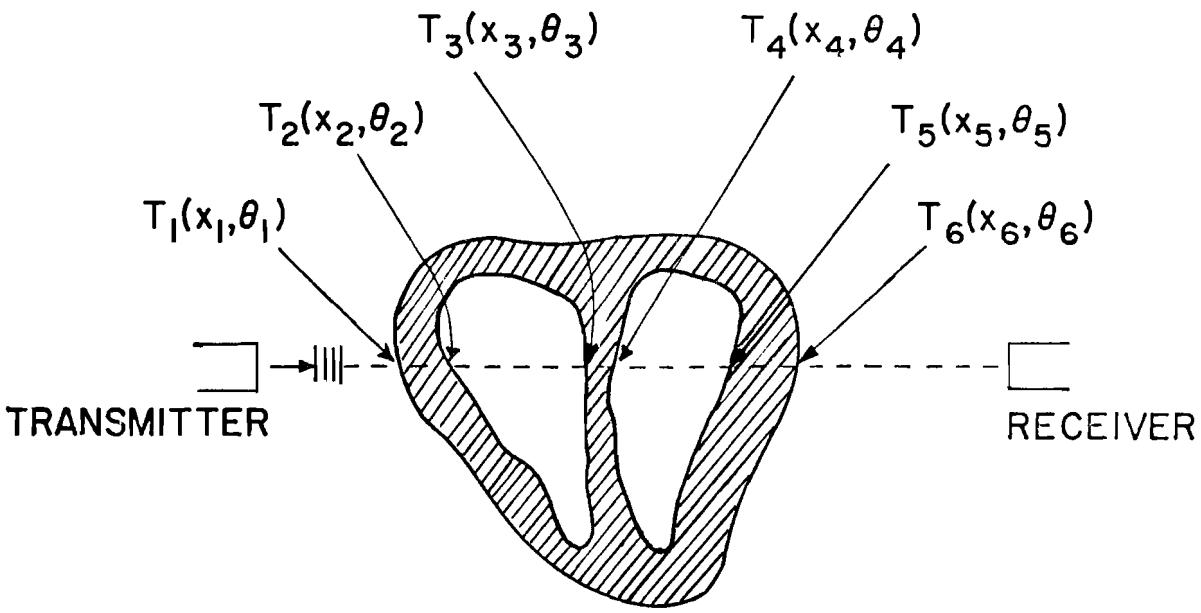
$$\ln P(\omega) - \ln P_0(\omega) = -\int_0^D \alpha(\omega,z)dz + \sum_{i=1}^{N-1} \ln T_i(\theta) \qquad (2)$$

Only the integral term in (2) is desired for attenuation tomography. Unfortunately, the sum of the logarithms of the transmission coefficients can introduce significant artifacts into the measurement. A solution to this problem is to make measurements at more than one frequency. For short ultrasonic pulses the attenuation coefficients of tissues depend upon frequency, while the transmission coefficients are independent of frequency. Thus, if measurements are made at two frequencies ω_1 and ω_2 and the results are logarithmically subtracted one obtains

$$\ln P(\omega_1) - \ln P(\omega_2) = -\int_0^D [\alpha_1(\omega_1,z) - \alpha_2(\omega_2,z)]dz + \begin{matrix}\text{normalizing} \\ \text{constant}\end{matrix} \qquad (3)$$

This quantity is independent of transmission coefficients and proportional to the slope of the ultrasonic attenuation versus frequency. By making measurements at more than two frequencies and applying this method a meaningful determination of the slope of the ultrasonic attenuation versus frequency is made. Only if a transmission coefficient equals zero will significant artifacts remain due to non-unity transmission coefficients.

REFLECTION LOSSES



$$P(x,\omega) = P_0(\omega)\left\{\exp\left[-\int_0^x \alpha(\omega,x')dx'\right]\right\}\left\{\prod_{i=1}^{N} T_i(x_i,\theta_i)\right\}$$

I II III

I Normalizing Factor

II Desired Measurement

III (Non-Unity) Transmission Coefficients

FIGURE 1.

REFLECTION LOSSES

Phase Cancellation

In the previous section a simple ray theory was developed. In practice, however, spatially extended transmitters and receivers must be used. If a standard piezoelectric element is used as the receiver, amplitude measurements may be degraded by the integrating nature of such an element. The instantaneous voltage produced by a piezoelectric receiver is proportional to the integral of the instantaneous ultrasonic pressure across the face of the transducer. Thus, for a plane wave at normal incidence to a plane piezoelectric element, the phase of the incident wave is constant across the face of the receiver so that an amplitude measurement of an ultrasonic pulse yields the correct value. If, however, the phase fronts incident upon the receiver are distorted in space, the amplitude measurement is degraded, i.e., phase cancellation occurs.

One way to minimize phase cancellation effects is to use a small piezoelectric element as the receiver to limit the area over which the incoming pulse must be integrated. Unfortunately, the magnitude of refraction effects is such that use of a single small aperture receiver is not feasible since the refracted beam can be missed entirely. An array of small piezoelectric elements offers some improvement, but a more fundamental solution which makes use of a CdS acoustoelectric transducer as the receiver is being developed in the Physics Department under separate funding.

A signal derived from the acoustoelectric effect is proportional to the incident intensity of ultrasound as opposed to the ultrasonic amplitude and phase. Thus, the acoustoelectric device is insensitive to phase cancellation. A large aperture acoustoelectric receiver requires only a single set of receiver electronics as opposed to the necessity of many parallel receiver circuits for a piezoelectric array of the same size. Integration of the acoustoelectric receiver into our tomographic scanner requires relatively straightforward modifications which are being carried out.

Refraction and Finite Beam Width

Refraction will occur whenever the ultrasonic wave propagates through media of differing ultrasonic phase velocity. Using the ray model presented earlier, if a ray of ultrasound is incident upon an interface between two media at an angle θ_1 from normal in medium 1, the new direction of propagation, θ_2, in medium 2 is

$$\frac{\sin \theta_1}{c_1} = \frac{\sin \theta_2}{c_2}$$

where c_1 and c_2 are the phase velocities in the respective media. Since the velocity of sound in various tissues may differ by five to ten percent, significant refraction can occur whenever the angle θ_1 becomes large. Total reflection occurs beyond the critical angle, i.e., whenever $(c_2/c_1) \times$

$\sin \theta_1 > 1$. Analysis of the refraction problem has been done for a uniform disk of material with velocity c_2, surrounded by a uniform medium with velocity c_1, taking finite beam width into account. This analysis indicates that if the transmitter beam is narrow, a receiver with a large aperture compared to the transmitted beam would minimize refraction losses if no phase cancellation occurs. This approach requires taking the finite beam width explicitly into account, which we propose to do in a manner analogous to the approach of Hurwitz[1] or Glover and Sharp.[2]

Tissue Anisotropy

Anisotropy of the ultrasonic attenuation coefficient and phase velocity has been reported for several types of soft tissue.[3] We have evaluated analytically the effect of such an anisotropy on tomographic reconstructions for an annulus of material where the anisotropy was either circularly or linearly directed. Computer simulations were performed also, and these correlated well with our analytic solutions. Results of these model studies suggest that an annular region exhibiting anisotropy is reconstructed in slightly distorted shape, but with significant artifacts induced in the numerical values of attenuation in both the region of the annulus and outside it. Further experimental work is necessary to determine the actual functional dependence and magnitude of any possible anisotropy in the attenuation coefficient of tissue and to evaluate the consequences for tissue characterization.

[1] H. Hurwitz, Jr., "Entropy Reduction in Bayesian Analysis of Measurements," Physical Review A, vol. 12, pp. 698-706, 1975.

[2] G. H. Glover and J. C. Sharp, "Reconstruction of Ultrasound Propagation Speed Distributions in Soft Tissue: Time-of-Flight Tomography," IEEE Transactions on Sonics and Ultrasonics, SU-24, pp. 229-234, 1977.

[3] W. D. O'Brien, Jr., "The Role of Collagen in Determining Ultrasonic Propagation Properties in Tissue," Acoustic Holography, vol. 7, 1977, to be published.

B-3. The CUTAR Scanner and Experimental Results

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Support: RR 00396
Washington University

The Computerized Ultrasonic Tomographic Attenuation Reconstruction (CUTAR) scanner was put into operation in February, 1977. The complete system was designed with the following features:

1) The stepping motor driven mechanical scanner with 0.066 mm translational and 0.03 degree rotational resolution is capable of scanning up to 15.0 cm dia. objects. Figure 1 shows the scanner configuration.

2) A modular analog system performs ultrasonic pulse generation and gated pulse sampling and detection (Figure 2). Analog processing is divided among numerous "building blocks" (gated peak detector, sampler, automatic gain controlled amplifier, gating logic), making possible extensive revision by simply exchanging, adding, or deleting modules. An automatic gain control loop under computer control adjusts the transmitter power to achieve approximately 80 db dynamic range at 5 MHz.

3) A PC-12 computer is equipped with high speed A/D and D/A interfaces, parallel digital input and output interfaces, PEP 400R grey level display, Versatec plotter for 16 grey level hardcopy generation, and the "intelligent stepping motor controller" to drive the scanner with a minimum of CPU overhead.

4) A FORTRAN software package (CUTARSYS) provides:

a) Multiple-frequency scanner operation,
b) Raw data pre-processing and display,
c) Filtered-back-projection reconstruction,
d) Automatic file handling and data manipulation,
e) Windowed reconstruction display and hardcopy generation,
f) Hardware testing, set up, and calibration,
g) Editing and handling of detailed descriptions of each scan performed,
h) Scan and reconstruction simulation for mathematical model testing.

New PC-12 file management and overlay packages developed with this system have been adapted for general PC-12 use (I-9). CUTARSYS is designed to be used by persons unfamiliar with computer operation.

Although adaptable to other schemes the present scanner configuration uses gated, narrow-band pulses of RF in the range of 2 to 8 MHz. A single

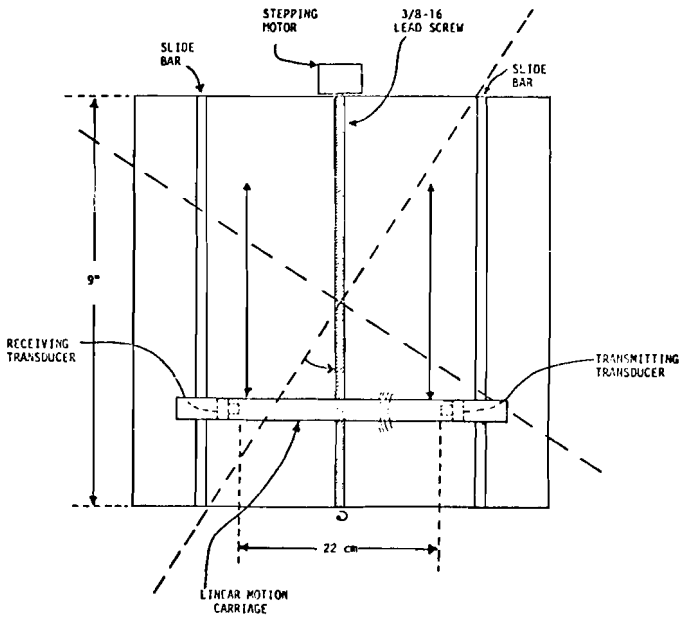

FIGURE 1.
Cutaway top view of scanner configuration. The portion shown is supported from above and rotates about the central axis. Transducer support arms extend down into the water tank from the linear motion carriage.

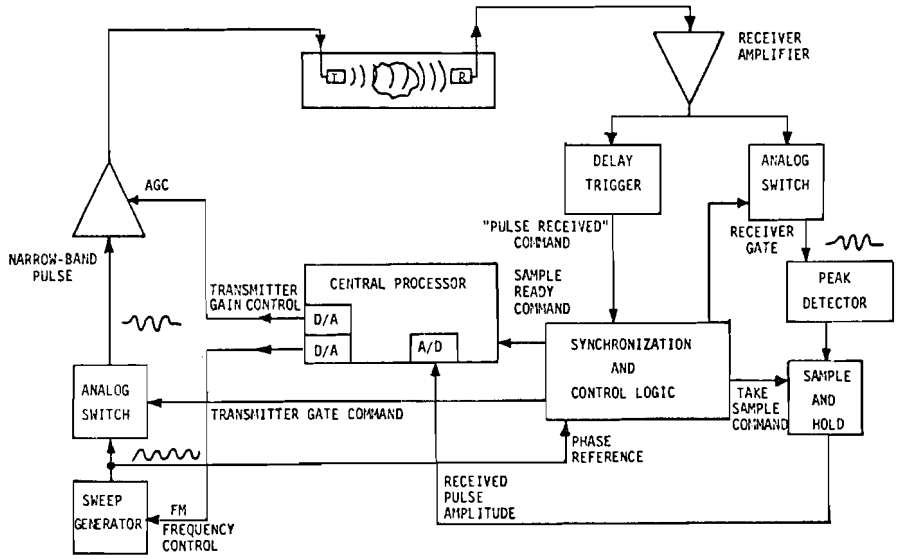

FIGURE 2.
Block diagram of the acquisition system.

unfocused broad-band piezoelectric transducer transmits the 2μs RF pulses in a wide but collimated beam. Directly opposite the transmitter an unfocused broad-band transducer acts as a receiver. Transmitters of 3/8" and 1/2" diameter have been used with receivers from 1/25" to 1/2" diameter. The received pulse triggers a threshold circuit, the signal is peak-detected and the resulting level stored in a sample-and-hold circuit. The analog level is digitized by a PC-12 A/D interface. The PC-12 adjusts the transmitted pulse amplitude to provide a received signal within a predefined range. A typical scan of 80 translations and 120 angular views requires 40 minutes.

Reconstructions have been performed by using the filtered back-projection method. The filter used assumes ideal sampling with no correction for finite beam width. Provisions for simple modification of this filter have been built into the software package.

Early experimental results from scans carried out with the prototype scanner are encouraging even though several problems are yet to be overcome. Table I shows results from two scans of a rubber glove filled with castor oil. Castor oil is a particularly good test object at the temperatures shown since its velocity of sound differs from that of the surrounding water bath by only 1%, making refraction and phase cancellation effects minimal. The accepted frequency dependence of $f^{5/3}$ was assumed in order to compare our attenuation measurements taken at 3 and 4.5 MHz with those reported for 1 MHz by Schwan.[1] Numerical values from the central regions of the glove fingers were used in this analysis. Agreement between our results and those of Schwan is excellent. Geometric definition of the glove fingers is good, with only a few edge artifacts and streaks in the background.

Table II shows results from several in-vitro scans of biological specimens. Exterior geometric definition of these specimens was good, but definition of interior features was only fair for the kidney and heart to poor for the liver. Significant edge artifacts and background streaking were present in all three reconstructions due to refraction effects and phase cancellation. Numerical values used in this analysis excluded obvious edge artifacts. The wide range of slope determinations for each specimen was probably due to refraction and phase cancellation effects for which no compensation was made.

TABLE I

Temperature	Freq. 1	Freq. 2	Present work (cm^{-1})	Schwan's results (cm^{-1})
18.5°C	3.0 MHz	4.0 MHz	0.108 ± .005	0.106
20.0°C	3.0 MHz	4.5 MHz	0.090 ± .015	0.096

TABLE II
EXCISED TISSUE

Specimen	Freq. 1	Freq. 2	Slope of attenuation coefficient vs frequency
calf heart	3.0 MHz	5.0 MHz	0.086 - 0.26 cm^{-1} MHz^{-1}
beef kidney	3.5 MHz	6.0 MHz	0.086 - 0.23 cm^{-1} MHz^{-1}
beef liver	3.5 MHz	5.5 MHz	0.076 - 0.23 cm^{-1} MHz^{-1}

(1) H. Schwan, Biological Engineering, McGraw-Hill, New York, p. 214, 1968.

B-4. PETT IV and Its Computer System

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The purpose of emission transaxial reconstruction tomography is to reproduce the radionuclide distribution in a cross-sectional slice of an object by external coincidence detection of annihilation radiation. Events are recorded when two 511 keV photons from positron annihilation are detected simultaneously in two detectors. Since the two 511 keV photons are emitted at 180°, this limits the field of view to activity lying in a well-defined region between the two detectors.

To evaluate the coincidence detection method for emission tomography, a prototype scanner was designed, constructed, and tested. This scanner, called PETT(1,2) (PR 11, B-7), showed that positron emission reconstruction tomography permits the visualization of structures which are not ordinarily perceptible with conventional nuclear medicine imaging devices. It also provides quantitative information about the distribution of radioactivity within the organ being imaged. Figure 1 demonstrates the linear response of the PETT numbers of specific activity of a radionuclide for two different sizes of phantoms.

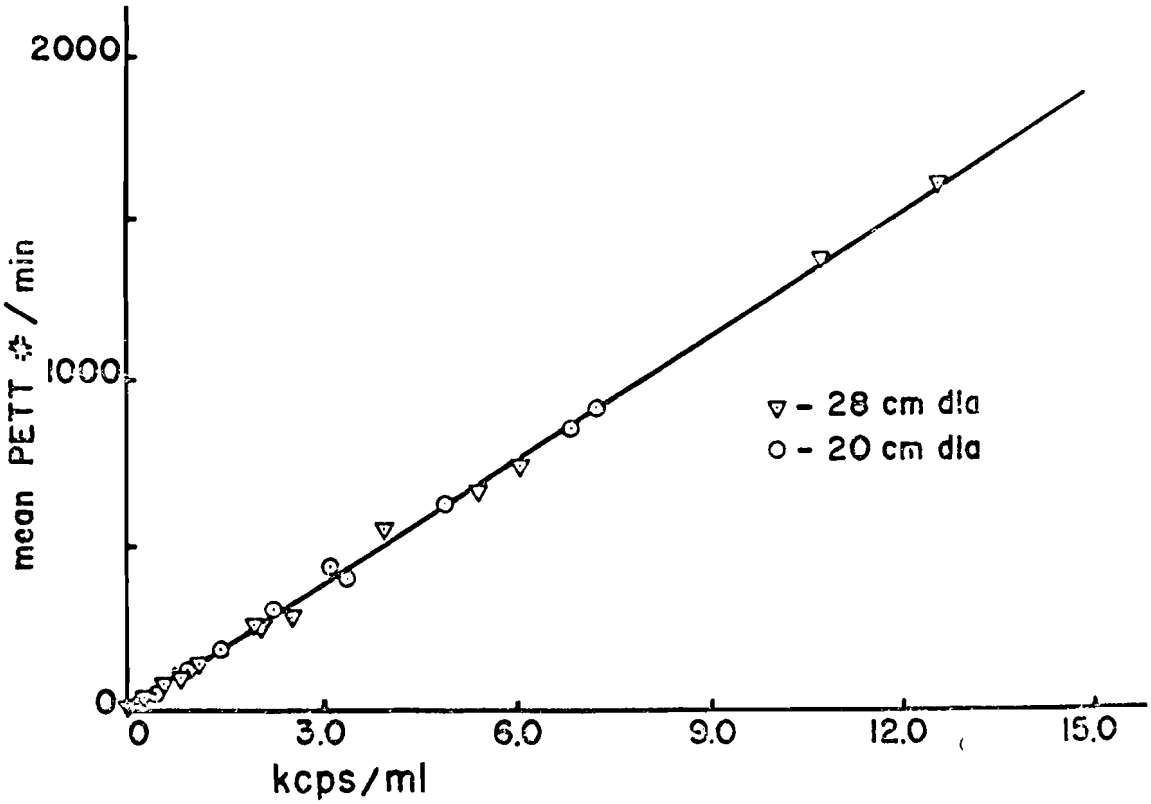

Figure 1. Linear response of the PETT numbers to varying specific activity of a radionuclide for two different sizes of phantoms.

A clinically usable scanner (PETT III) was designed, built, and tested[3] (PR 12, B-1) based on the principles used in the prototype PETT. PETT III employs 48 NaI(Tl) scintillation detectors placed about a cross section in a hexagonal array (Figure 2). Six sets of eight detectors are mounted on platforms capable of rectilinear motion, with the six platforms of detectors mounted on a gantry that provides a rotational motion. Each detector on a platform is in coincidence with the eight detectors on the opposite platform, thus increasing the detection efficiency of the scanner.

Extensive studies on patients and animals have been carried out with PETT III in the areas of neurology and cardiology.[4,6] These studies have indicated that important information for diagnosis and treatment of disease can be obtained by PETT-type scanners in a clinical environment.

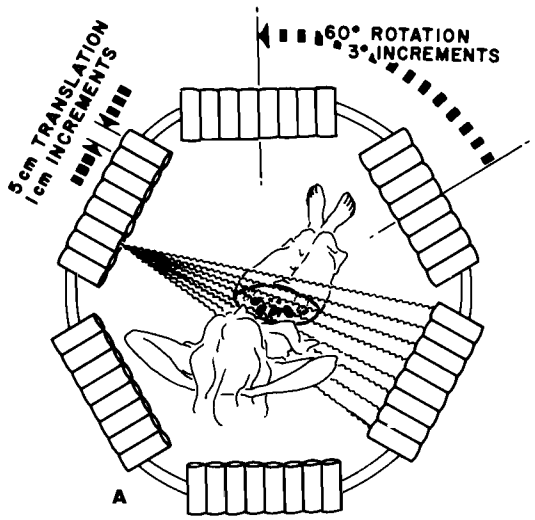

Figure 2. Block diagram of scintillation detector array of PETT III.

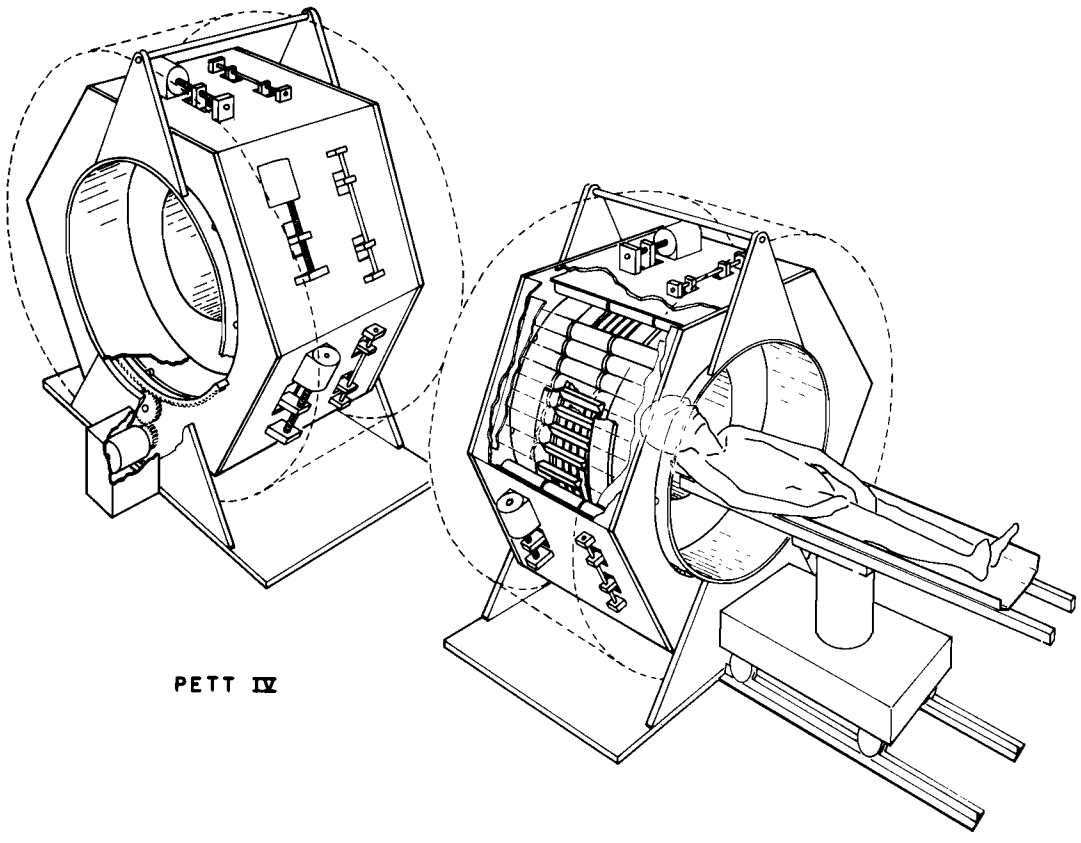

Figure 3. Pictorial representation of the PETT IV system.

A new scanner, PETT IV, (Figure 3), has been designed and constructed for the study and assessment of myocardial infarcts in the Cardiac Care Unit of the Department of Cardiology. This scanner is designed using PETT III concepts and employs 48 NaI(Tl) detectors arranged in a hexagonal array with eight detectors on each side. Each detector is 2 inches in diameter by 6.75 inches, with a photomultiplier tube at each end.

A novel technique has been used in PETT IV for the collection of four slices simultaneously without employing four sets of detectors, i.e., one for each slice. Collecting four slices simultaneously reduces scan time and, thereby, limits discomfort to the critically ill patient. This technique uses the principles on which the gamma camera is based but modifies them from two-dimensional to one-dimensional positioning along a detector. A gamma ray impinging on a NaI(Tl) crystal will cause the crystal to fluoresce at the point of impact, the amount of light generated being proportional to the energy deposited by the gamma ray in the crystal. In our detectors (Figure 4) this light is collected by two photomultiplier tubes, one at each end, and converted into an electrical pulse, the amplitude of which is proportional to the energy delivered by the gamma ray and the position at which it interacts with the crystal. The pulse heights I_1 and I_2 for the photomultiplier tubes PM1 and PM2 are shown to vary with the positions of the gamma ray source along the length of the crystal, as shown in the bottom part of Figure 4. The energy and position of the gamma ray interaction within the detector are given by: Energy $\propto(I_1 + I_2)$ and position $\propto(I_1/I_2)$. We have designed a very fast and simple circuit which computes the ratio of I_1 to I_2 and digitizes it into two binary bits within 150 nanoseconds. This, together with special lead septa in front of the detectors, has enabled us to create four distinct sections for the four slices. Each slice has a resolution of approximately 1.5 cm FWHM and is separated by a distance of 3.81 cm.

Computer System

PETT IV is interfaced to an Interdata 7/32 computer with 256 K bytes of memory and floating point arithmetic. The computer system includes two Pertec 10 M byte disks, a Pertec 75 IPS/800 BPI tape drive, a Versatec line printer, and a specially designed video image-display system. The display incorporates a 256 × 256 × 10 bit solid-state memory with fast on-line arithmetic capability for image enhancement. A block diagram of the computer system is shown in Figure 5.

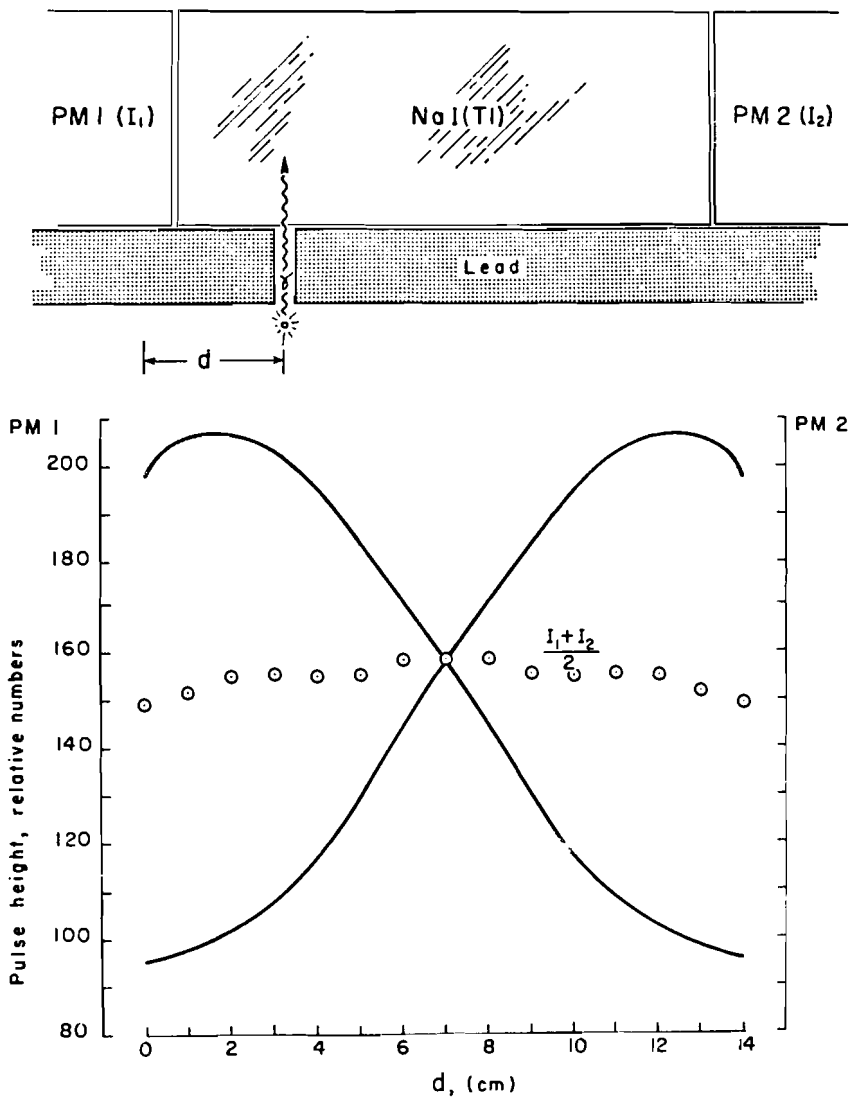

Figure 4. (TOP) Cross-section of a PETT IV detector. (BOTTOM) Pulse height variations observed in the detector with respect to the source position d.

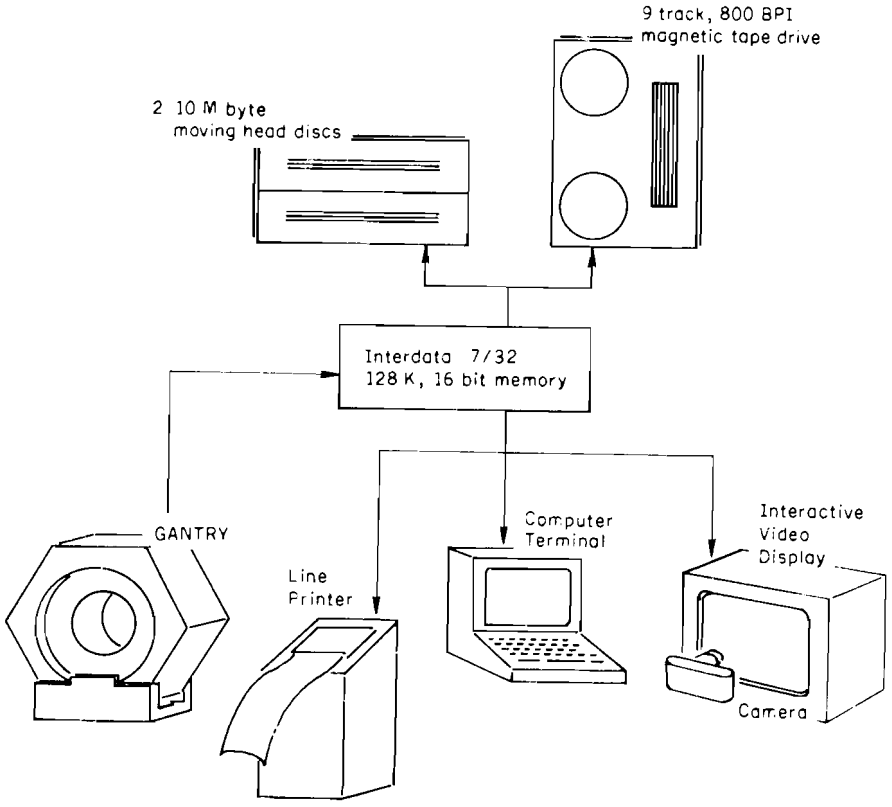

Figure 5. PETT IV computer system.

Experience with the PETT III computer system has shown that the computing requirements for positron CT scanners can be divided into four major tasks:[7,8] (1) data collection and gantry control, (2) preprocessing of collected data, (3) reconstruction of image, and (4) image display. Tasks (1) and (4) require very little computation time (<5% of real time), whereas tasks (2) and (3) utilize considerable CPU time. Table I lists the four tasks and their CPU requirements for a typical PETT III scan. It also indicates that for a complete scan process the CPU is active for less than 50% of the real time. By overlapping the processing tasks with data collection and display, the CPU can be kept active for greater than 90% of real time. This effectively increases the processing speed by at least a factor of two, depending upon the scan time and the number of slices collected. To achieve this goal we are using a multitasking operating system from Interdata (OS 32/MT), running four foreground tasks and a background task area dedicated to software development.

TABLE 1

CPU Time Requirements for a Typical PETT III Scan

Task	Real Time	% CPU Time/ Real Time
Data collection	2-8 min[1]	<5%
Preprocessing	0.5 min	>80%
Reconstruction	1.5 min	>95%
Image Display	0.5-5 min[2]	<5%

[1]Scan time is dependent on the nature of the study.

[2]Image display time dependent on the user's ability to "read" the scan.

(1)M. E. Phelps, E. J. Hoffman, N. A. Mullani, and M. M. Ter-Pogossian, "Application of Annihilation Coincidence Detection to Transaxial Reconstruction Tomography," Journal of Nuclear Medicine, vol. 16, pp. 210-224, 1975.

(2)M. M. Ter-Pogossian, M. E. Phelps, E. J. Hoffman, and N. A. Mullani, "A Positron Emission Transaxial Tomograph for Nuclear Imaging (PETT)," Radiology, vol. 114, pp. 89-98, 1975.

(3)E. J. Hoffman, M. E. Phelps, N. A. Mullani, C. S. Higgins, and M. M. Ter-Pogossian, "Design and Performance Characteristics of a Whole-Body Positron Transaxial Tomograph," Journal of Nuclear Medicine, vol. 17, pp. 493-502, 1976.

(4)M. M. Ter-Pogossian, E. S. Weiss, R. E. Coleman, and B. E. Sobel, "Computed Tomography of the Heart," American Journal of Roentgenology, vol. 127, pp. 79-90, 1976.

(5)M. M. Ter-Pogossian, E. S. Hoffman, E. S. Weiss, R. E. Coleman, M. E. Phelps, M. J. Welch, and B. E. Sobel, "Positron Emission Reconstruction Tomography for the Assessment of Regional Myocardial Metabolism by the Administration of Substrates Labeled with Cyclotron-Produced Radionuclides," presented at the Conference on Cardiovascular Imaging and Image Processing: Theory and Practice, Stanford University, Stanford, California, 1975.

(6)M. M. Ter-Pogossian, M. E. Phelps, E. J. Hoffman, and M. E. Raichle, "A Positron Emission Transverse Tomograph (PETT) for the Three-Dimensional and Non-Invasive Measure of Cerebral Hemodynamics and Metabolism," In Blood Flow and Metabolism in the Brain, Churchill Livingstone, Edinburgh, 1975.

(7) N. A. Mullani, R. E. Hitchens, and C. S. Higgins, "Computer Systems Requirements for Tomography," Proceedings of the Sixth Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine, Society of Nuclear Medicine, 1976.

(8) C. S. Higgins, N. A. Mullani, E. J. Hoffman, M. E. Phelps, and M. M. Ter-Pogossian, "System Software for a Positron Emission Transaxial Tomograph (PETT III)," Proceedings of the Sixth Symposium on Sharing of Computer Programs and Technology in Nuclear Medicine, Society of Nuclear Medicine, 1976.

B-5. Performance Characteristics of PETT IV

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Support: RR 00396
HL 13851
HL 17646
NS 06833

Performance characteristics which are important in evaluating a positron computerized tomographic scanner and some preliminary results obtained with PETT IV follow. The major performance characteristics important to a user are:

(1) resolution,

(2) sensitivity,

(3) coincidence resolving time,

(4) amount of scattered radiation accepted,

(5) linearity of both spatial and activity distribution.

Resolution and sensitivity are the major indicators of the performance of a scanner because they reflect the contributions of the other parameters, e.g., resolution is degraded and sensitivity increased if the scatter contribution is high. Resolution and sensitivity are interrelated according to

$$\text{Sensitivity} \propto (\text{resolution})^4$$

Therefore, in a photon limited case such as with emission scanners, resolution should not be improved without a collateral improvement in the detection system to maintain necessary sensitivity of the scanner. It is also important to make a distinction between the inherent resolution of the detection system and the reconstructed resolution since the latter is usually poorer due to sampling, noise, scatter, choice of algorithm, etc.

Although no standard format for the evaluation of these parameters exists, most of the manufacturers and builders of emission scanners have tried to standardize on a 20 cm diameter test object approximating the human brain. The sensitivity of PETT IV for a 20 cm phantom is approximately 6000 counts/sec/microcurie per slice for an inherent resolution of 1.5 and 1.6 cm FWHM, as shown in Figures 1 and 2. The reconstructed resolution, as measured by a line spread function, is approximately 1.7 cm for a 2 cm source in plastic (Figure 3). The sources are separated by distances of 2, 3, 4, and 5 cm along the radius.

The coincidence resolving time of PETT IV has been set at 20 nanoseconds even though the detection system is capable of 14 nanoseconds FWHM. The extra six nanoseconds allows for some variation from detector to detector. Further work is being carried out to evaluate the linearity and scatter contribution for various objects.

Figures 4 and 5 demonstrate the imaging capabilities of PETT IV for human studies. Figure 4 is a brain scan of the brain blood volume, using ^{11}C-carboxyhemoglobin, and Figure 5 shows the uptake of ^{11}C-palmitate in the left ventricular muscle of the heart.

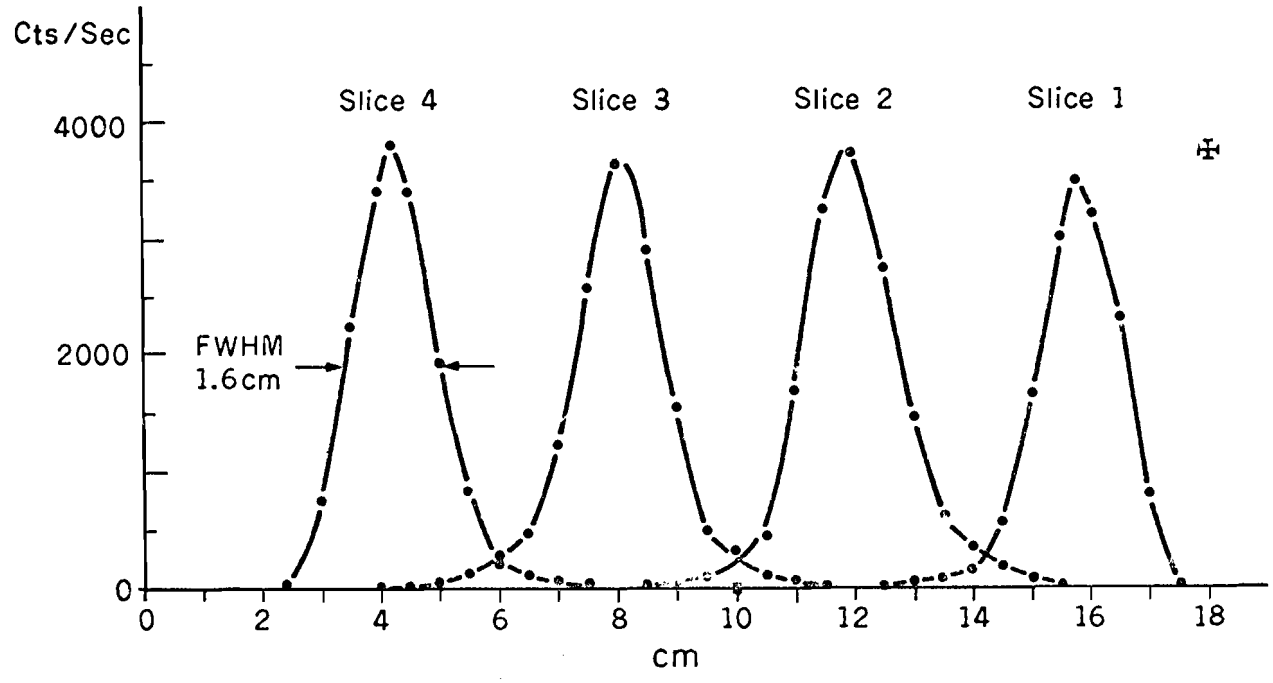

Figure 1. PETT IV LSF for the slice thickness with 1.5 mm ^{64}Cu source detector 3x3 with source at center.

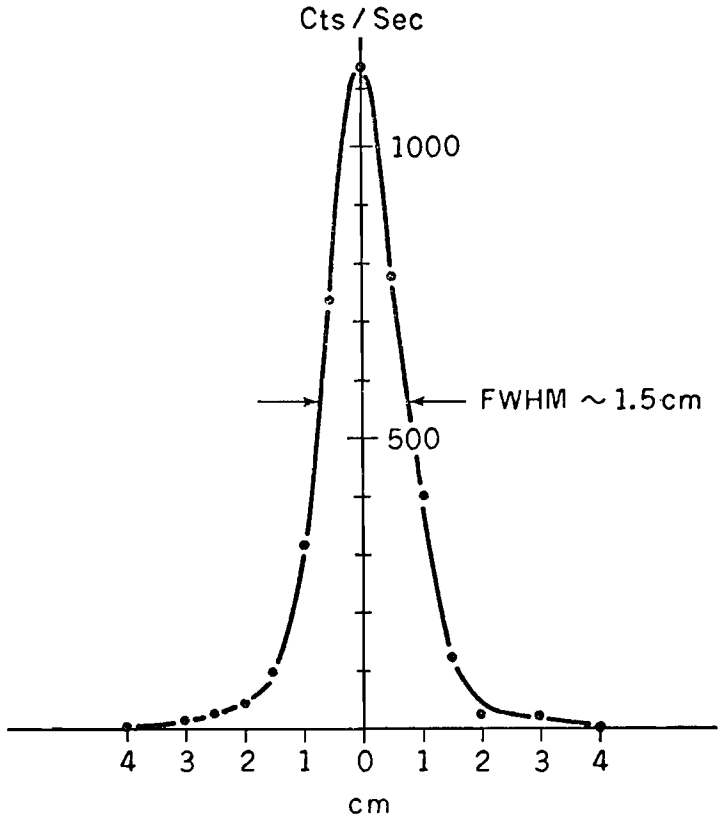

Figure 2. PETT IV LSF in air in the tomographic plane.

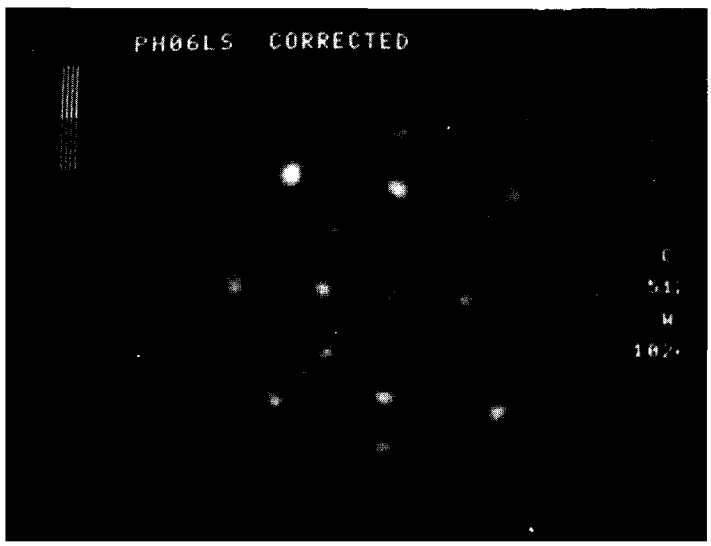

Figure 3. PETT IV. Linespread function.

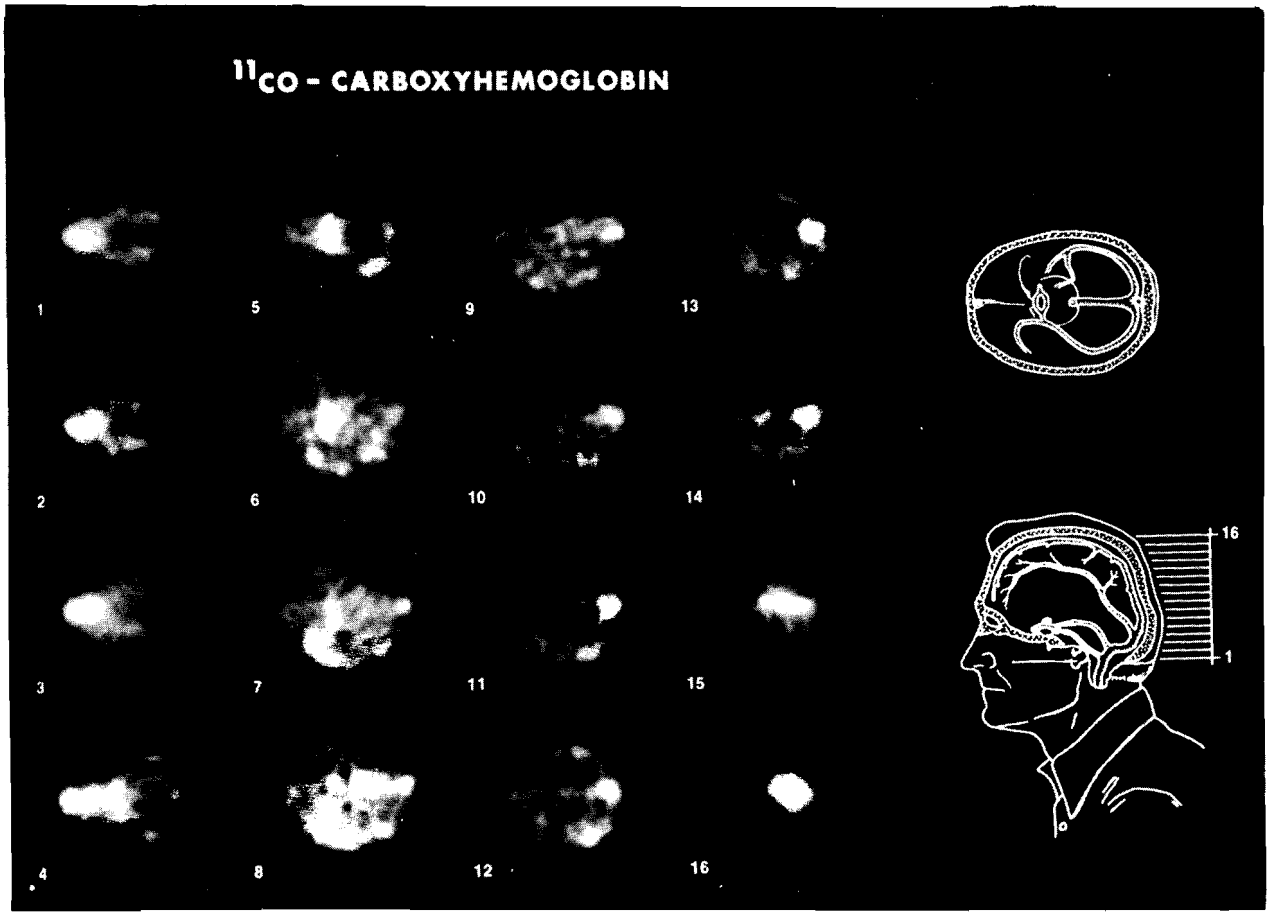

Figure 4. Typical brain study with ^{11}CO.

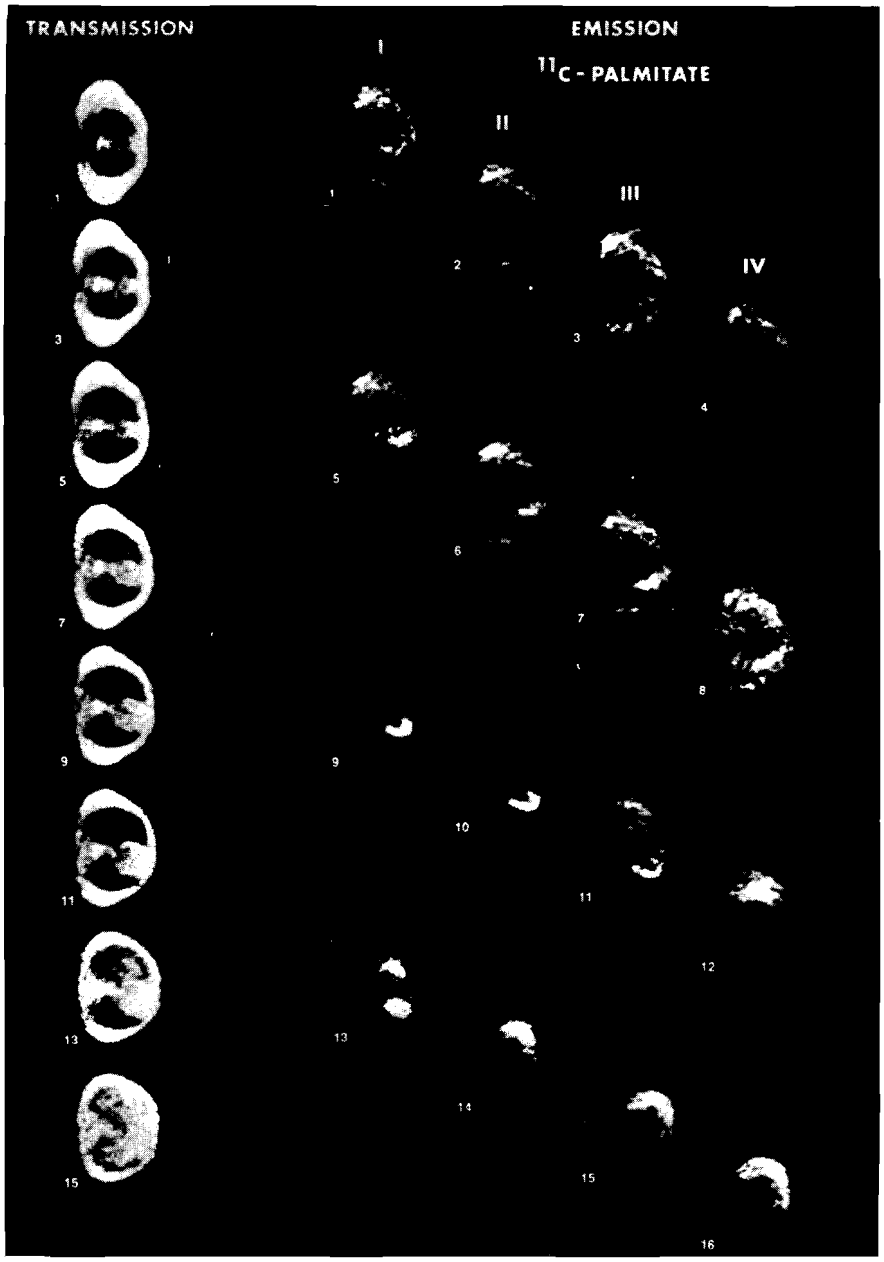

Figure 5. Typical heart study with ^{11}C-palmitate.

B-6. External Detection and Tomography of Ischemic Myocardium

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During the past year continuing studies were undertaken to visualize ischemic myocardium quantitatively,[1,12] based on the principle that accumulation of free fatty acid (FFA) is attenuated in ischemic tissue and ceases in zones of infarction. This principle was substantiated in studies reported previously (PR 12, A-4), in which it was demonstrated that external detection of ^{11}C-labeled FFA was possible in the isolated perfused heart and that the extraction fraction of this physiological substrate of myocardium diminished in association with ischemia. The overall goal of the project was to develop quantitative techniques for evaluation of jeopardized ischemic myocardium *in vivo*, as well as quantification of the extent of myocardial infarction.

We have previously shown that isovolumically beating rabbit hearts extract ^{11}C-labeled FFA under conditions of normal flow, but that extraction diminishes after 30 minutes of low flow from approximately 40 to less than 3%. Myocardial avidity for ^{11}C-palmitate after intravenous injection of the radioactively labeled tracer was demonstrated in dogs given 5 mCi of the agent intravenously and then studied with a rectilinear scanner. Subsequently, diminished ^{11}C-palmitate uptake in zones of myocardium rendered ischemic for 20 minutes prior to reflow was delineated with electrocardiographically gated positron emission transaxial tomography, again after intravenous injection of the tracer.[2]

Subsequently these observations were extended to intact canine hearts *in vivo*. Myocardial infarction was quantified externally by positron emission transaxial tomography in 20 closed chest dogs.[3,6] The infarct delineated in each tomographic cross section was compared to the area of infarction in the corresponding gross specimen as determined by planimetry of photographs of gross morphology and the distribution of infarction detectable histologically. In addition, tomographic results were compared to the regional extent of infarction detected by analysis of myocardial creatine kinase (CK) activity. The percentage of infarcts in tomographic reconstructions (ranging from 0 to 68%) of cross sections of the left ventricle *in vivo* correlated closely with depletion of myocardial CK activity ($r = .93$) and with morphometric estimates of infarct in corresponding cross sections of the ventricle ($r = .92$).

Quantitative interpretation of results obtained by positron emission transaxial tomography required delineation of the metabolic pathways of the radioactively labeled fatty acid administered intravenously. For this reason studies have been undertaken during the past year with isolated perfused hearts in which the distribution of ^{14}C- and ^{11}C-palmitate into specific metabolic pools within myocardial cells could be examined.(7,8) Twenty-three rabbit hearts were equilibrated for 20 minutes at high flow (5 ml/g) without tracer before exposure to ^{14}C- and ^{11}C-palmitate at low flow (1 ml/g) for 15 minutes or less (early ischemia), or 30 minutes (late ischemia). In control hearts high flow was maintained during the corresponding interval. Neutral and polar lipids in extracts prepared from fast-frozen myocardium were separated chromatographically and the specific radioactivity of each fraction was determined by thin layer radiochromatography. Total phospholipid content remained constant (107 to 118 μmoles/g dry) and the specific activity remained low (less than 1%). Total triglycerides increased by 73% after 30 minutes of ischemia. Augmented incorporation of exogenous FFA was evident, based on the increase in specific radioactivity of the triglyceride pool in hearts exposed to ischemia for 15 minutes or less. Parallel changes were detectable externally with ^{11}C-FFA. These results suggest that increased FFA uptake may accompany early ischemia and be amenable to quantification by positron emission transaxial tomography in vivo.

During the past year positron emission transaxial tomography to detect ischemic injury in vivo was applied successfully to patients with previous remote myocardial infarction.(9,12) Ten normal subjects and ten patients with infarction occurring within one year of the study were evaluated. Tomography was performed with 48 NaI detectors programmed through rotational and translational motion to obtain computer-reconstruction images of the distribution of intravenously injected, cyclotron-produced, positron-emitting ^{11}C-palmitate in 1.5 cm thick cross sections of the ventricle from apex to A-V valve (see also B-4). Within six minutes after intravenous injection of 5 to 10 mCi of the tracer, each normal subject exhibited homogeneous distribution of ^{11}C-palmitate throughout the entire cross section of ventricular myocardium with clear delineation of both ventricular free walls and the intraventricular septum. In each of the patients with transmural infarction (with persistent Q waves on the electrocardiogram) depression of ^{11}C-palmitate accumulation was shown to correspond to the electrocardiographic locus of infarction. In each of two patients with subendocardial infarction (without Q waves), intramural depression of accumulation of ^{11}C-palmitate was evident. Diminished accumulation of ^{11}C-palmitate was considered to be present only when the regional count rate was less than 50% of the count rate in adjacent normal myocardium. In parallel canine experiments, similar regional depression of ^{11}C-palmitate accumulation was detectable tomographically and found to correlate closely with infarction in the corresponding cross sections which were estimated morphometrically and biochemically. Thus, positron emission transaxial tomography in patients appears to facilitate detection and quantification of infarction and should permit objective evaluation of interventions designed to protect jeopardized ischemic myocardium.

(1) P. B. Corr and B. E. Sobel, "Automated Data Processing: An Essential Decision-Making Aid in the Treatment of Acute Myocardial Infarction," in Advances in Cardiology, vol. 20, John H. K. Vogel, ed., S. Karger, Basel, Switzerland, pp. 54-71, 1977.

(2) E. S. Weiss, E. J. Hoffman, M. E. Phelps, M. J. Welch, P. D. Henry, M. M. Ter-Pogossian, and B. E. Sobel, "External Detection and Visualization of Myocardial Ischemia with ^{11}C-substrates In Vitro and In Vivo," Circulation Research, vol. 39, pp. 24-32, 1976.

(3) E. S. Weiss, S. A. Ahmed, M. J. Welch, J. R. Williamson, M. M. Ter-Pogossian, and B. E. Sobel, "Quantification of Infarction in Cross Sections of Canine Myocardium In Vivo with Positron Emission Transaxial Tomography and ^{11}C-Palmitate," Circulation, vol. 55, pp. 66-73, 1977.

(4) E. S. Weiss, M. J. Welch, M. M. Ter-Pogossian, C. S. Higgins, and B. E. Sobel, "Non-invasive Quantification of Myocardial Infarction with Positron Emission Transaxial Tomography," in Proceedings of the Conference on Computers in Cardiology, IEEE Catalog No. 76 CH 1160-1C, St. Louis, Missouri, pp. 41-44, 1976.

(5) B. E. Sobel, E. S. Weiss, and M. M. Ter-Pogossian, "Early Quantitative External Detection of Myocardial Infarction with ^{11}C-Fatty Acids," presented at the Fifteenth Annual Meeting of the Association of University Cardiologists, Inc., Phoenix, Arizona, January 1976 (abstract).

(6) E. S. Weiss, M. J. Welch, M. M. Ter-Pogossian, and B. E. Sobel, "External Quantification of Myocardial Infarction In Vivo," Clinical Research, vol. 24, p. 422A, 1976 (abstract).

(7) A. K. Robison, V. A. Hansen, and B. E. Sobel, "Accumulation of Lysophosphatides, Potential Mediators of Irreversible Injury in Ischemic Myocardium," Circulation, in press (abstract).

(8) C. W. Loh, A. K. Robison, M. J. Welch, and B. E. Sobel, "External Detection of Early Effects of Ischemia with Labeled Fatty Acid," Circulation, in press (abstract).

(9) B. E. Sobel, E. S. Weiss, M. J. Welch, B. A. Siegel, and M. M. Ter-Pogossian, "Detection of Remote Myocardial Infarction in Patients with Positron Emission Transaxial Tomography and Intravenous ^{11}C-Palmitate," Circulation, vol. 55, pp. 853-857, 1977.

(10) E. S. Weiss, M. J. Welch, M. M. Ter-Pogossian, and B. E. Sobel, "Non-Invasive Delineation of Myocardial Infarction in Man," American Journal of Cardiology, vol. 39, p. 316, 1977 (abstract).

(11) B. E. Sobel, "External Quantification of Myocardial Ischemia and Infarction with Positron-Emitting Radionuclides," in Advances in Cardiology, vol. 22, John H. K. Vogel, ed., S. Karger, Basel, Switzerland, in press.

(12) E. S. Weiss, B. A. Siegel, B. E. Sobel, M. J. Welch, and M. M. Ter-Pogossian, "Evaluation of Myocardial Metabolism and Perfusion with Positron-Emitting Radionuclides," Progress in Cardiovascular Diseases, in press.

C. Clinical Pathophysiology and Patient Monitoring

BCL activities specifically addressed to clinical pathophysiology began in 1970, the year after the Argus system for on-line cardiac arrhythmia analysis became operational in the Barnes Hospital Coronary Care Unit. In 1973 a minicomputer based patient monitoring system was installed in the Barnes Hospital Cardiothoracic Surgical Intensive Care Unit (SICU) to bring state-of-the-art continuous digital processing of physiologic signals to the bedside. The system provides acquisition and analysis of transduced patient signals for derivation, storage, retrieval, and display of multiple variables relevant to clinical management, as well as to study the acutely ill. Tasks have been assigned to specialized hardware, a dedicated minicomputer (PC-1200), and support personnel, in recognition of their respective strengths and weaknesses, in order to achieve a highly reliable yet cost-conscious system. Specialized hardware components include a unique video display system and an advanced communication system designed for high-performance local and remote digital data transmission. Substantial effort was devoted to assuring data integrity, in recognition of the clinical hazards of giving misleading information and of the fragility of system credibility on initial exposure to clinical personnel. After four years of continuous use the system is regarded highly, is well used for clinical purposes, and has set demanding standards in the local community for its planned replacement with a commercial system in new care units now on the drawing board.

The presence of the SICU system has heightened the awareness of clinical investigators to the value of on-line digital signal processing and external control in pathophysiologic research. To satisfy their demands a more flexible clinical physiologic research cart (CPRC) was implemented two years ago. For practical reasons the CPRC has relied on a communication link to the SICU system for mass storage and display generation, but otherwise offers stand-alone capability for acquiring, processing, and retrieving data via keyboard interaction through an inboard TI-980 minicomputer. Experience indicates the desirability of now separating more clearly the clinical and research functions of the SICU and CPRC systems respectively. Current uses of the CPRC and/or SICU systems include supplementary monitoring of patients in an SICU annex, pulsatile perfusion studies in an animal laboratory, and therapeutic trial of theophylline for apnea of prematurity in a neonatal intensive care unit.

The involvement of BCL personnel in the development of these systems has led naturally to consultation requests regarding patient-monitoring systems from various clinical departments within the medical school, Barnes Hospital, and other hospitals in the St. Louis community. Recent efforts to honor such inquiries have been in the areas of defining the overall needs for a major hospital addition, planning an intensive care unit at another hospital, and selecting and evaluating a patient-telemetry system.

C-1. Cardiothoracic Surgical Intensive Care Unit System

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Support: RR 00396
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As noted last year (PR 12, C-1), plans to expand the Cardiothoracic Surgical Intensive Care Unit (SICU) patient-monitoring system were abandoned in favor of maintaining the current system until 1980 when the unit will be enlarged and moved to a new location. With this in mind, the SICU software was reorganized during the past year in order to simplify its maintenance by taking full advantage of the current PC-1200 operating system. At the time the SICU system was implemented, the PC-1200 operating system contained only an absolute assembler, which required that all communication between individual modules and all access to data outside a module be accomplished by absolute memory location. As a result, much care was needed when changing the software to insure that any locations affected by the change, such as module entry points, were properly addressed. The absolute addressing involved, and the use of 8K of core memory also necessitated a rather cumbersome overlay structure requiring that disk-resident background modules be sectioned on the disk at predetermined locations.

By accomplishing all inter-module communication through external references and utilizing 12K of core memory, all address resolutions between modules are done by the PC-1200 linking loader at load time, which eliminates the error-prone procedure of manually insuring current address resolution. The overlay structure for disk-resident background modules was simplified to take advantage of the PC-1200 operating system features. In addition, several modules were upgraded to improve execution, and modules were added to monitor system performance characteristics continuously. This reorganization was completed in March, 1977, with no degradation in system performance or reliability.

Training activities have continued as necessary to meet the rapid turnover of nursing personnel and the medical and biomedical engineering students who serve as part-time monitoring technicians. Now that the system and its clinical usage have matured, discussions have been initiated with Barnes Hospital Administration and the Nursing Service concerning their taking over responsibility for routine use of the system, as well as packaging of the BCL-designed patient-transducer fluid interface.

Utilization data for the four-bed unit continue to be sampled as shown below:

5 months beginning:	Occupancy as % of capacity (24-hr. day; 7-day week)	Average length of stay (days)
Jan. 1973	76	3.2
Jan. 1974	77	2.6
Jan. 1975	83	2.3
Jan. 1976	82	2.7
Jan. 1977	77	2.8

As noted for last year, the trend toward reduced occupancy and longer lengths of stay is felt to result from more effective use of a three-bed "step-down" unit which was initiated in late 1975. The four-bed acute-care unit, thereby, is better dedicated to the most critically ill. In addition, one of the cardiothoracic surgeons has substantially reduced the amount of cardiac surgery he performs.

The engineering evaluation continues as before with every system failure as carefully documented as the pressures of clinical usage will allow. A gratifying record of over 2000 hours between unintentional interruptions of monitoring was established in the second year of system operation, but was then spoiled by corrosion of untinned integrated circuit leads (in sockets) during the third year. Their subsequent replacement by ICs from a different manufacturer has resulted in improved reliability. Although the mean time between failures was only 720 hours for the last six months, three of the failures occurred in rapid succession and were due to a known memory weakness, the repair of which was deferred purposely. As in the past, the system runs 24 hours a day without any "down time" for preventive maintenance. Core dumps with software analyses continue to be important for identifying hardware failures.

C-2. Apnea in the Newborn

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Apnea of prematurity is a poorly understood but common problem among premature infants, particularly those weighing less than 1500 grams. It is characterized by the complete cessation of respirations for periods greater than 15 to 20 seconds and is usually associated with a fall in heart rate to less than 100. Treatment with theophylline promises to be an effective and safe alternative to mechanical ventilatory support which carries substantial risk of pneumothorax.

A study of the pharmacokinetics of theophylline and of its therapeutic effectiveness for apnea is in progress at St. Louis Children's Hospital in the Department of Neonatology. Needed to correlate changes in apneic episodes and heart rate with blood levels of theophylline was a method for recording and measuring apneic episodes and their duration, along with heart rate, over a representative period of time, a task best suited to an automatic data-processing system. Real-time processing of the physiologic parameters required a system which was flexible enough to allow for rapid hardware and software development, and was acceptable to the clinical personnel in the Neonatal Intensive Care Unit (NICU). Since no such system exists in the medical center, it was decided to record the infants' ECG and respiratory signals on analog tape for off-line processing on the SICU prototype system at BCL.

The apnea monitoring project consisted of two phases, collection and digitization of infant ECG and respiratory signals, which was mainly a hardware effort, and interpretation of the digitized signal to determine periods of apnea, which was a programming effort. After a premature infant in the NICU was identified as apneic, his ECG and respiratory signals (measured by thoracic impedance) were recorded using an FM analog tape recorder. The recordings consisted of 24-hour intervals covering both pre- and post-theophylline administration. The tapes were then brought to BCL where they were played back and processed in real time.

The ECG and respiratory signals were preprocessed using hardware filters. The ECG signal was passed through a low-pass filter in order to broaden the narrow infant QRS complex so that the algorithm developed for the detection of adult QRS complexes could be used. Since preprocessing the respiratory signal was necessary because of the low signal-to-noise ratio in the thoracic impedance measurement, a bandpass filter was used to

extract the respiratory signal from troublesome noise. Processing the tapes to determine periods of apnea required two programs, one to read the digitized analog signals and calculate heart and respiratory rates, and another to identify, sort, and display the periods of apnea. Heart rate was derived from the ECG signal, which was processed by using the program for QRS detection developed for use in the cardiothoracic surgical intensive care unit. Several techniques for interpreting the respiratory waveform were attempted in an effort to cope with frequent baseline shifts, widely varying signal amplitude, frequency, and noise. Attempted strategies included the development of adaptive criteria based on time-outs and the frequencies and amplitudes of previous breaths. No method or combination of methods for automatic criteria generation and adjustment was found to contend satisfactorily with the vagaries of the impedance signal. The respiratory signals were processed, therefore, using a simple max-min detection and user-selectable amplitude-threshold criteria for breath detection. During processing, all computer-detected periods of apnea (>10 seconds) were automatically recorded on a strip-chart for subsequent human editing.

Once the algorithms for processing the ECG and respiratory signals were established, a first-pass assembly language program was constructed, using an interrupt scheme which allowed for sampling the ECG at 240 samples per second and the respiratory signal at 120 samples per second. The output of the first pass was the recording on LINC tape of one beat-to-beat interval and one breath-to-breath interval every second. The LINC tapes were then processed using a FORTRAN program to tabulate the 24 hours of data in 15 minute segments, giving for each segment the average heart and respiratory rates, along with the numbers of 5-, 10-, 15-, and >20-second periods of apnea. The resulting data were found to be quite satisfactory for the purpose of the study.

C-3. Clinical Physiologic Research Cart

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The Clinical Physiologic Research Cart (CPRC) was implemented two years ago in order to address a class of pathophysiologic research needs requiring more equipment mobility and data-processing flexibility than were reasonable to provide via the basic SICU system. In addition, the presence of the cardiothoracic SICU system had generated enthusiasm in other clinical disciplines for such a capability.

The CPRC has also served as an experiment in remote communication between minicomputer systems in the hospital environment, provision for which was originally designed into the local high-speed communication bus for the patient-monitoring system. Included in the cart is a minicomputer (TI-980) interfaced to components providing a broad range of input/output functions appropriate to physiologic data acquisition and display, as well as for digital control of external devices. When the CPRC was implemented, practical considerations dictated that neither mass-storage nor display-generation hardware be included, but these functions would be provided instead by the SICU system through full-duplex serial communication link and a video coaxial cable. For studies now in progress, lines have been run to a 3-bed SICU annex and to an animal laboratory in another building. In its present configuration the CPRC is being shared between supplementary patient monitoring in the annex and pulsatile-perfusion studies in collaboration with the Division of Cardiothoracic Surgery.

The SICU/CPRC experience confirms that there is a class of applications with sufficient commonality in data acquisition, analysis, display, storage, and control needs that can be met by a mobile system without sacrificing user convenience, economy, or compactness. Furthermore, it is clear that within this application class even a small library of software routines can be adapted to serve multiple uses without requiring excessive programming overhead or uncommon ingenuity. To this end, a software architecture which minimized interdependence of highly modular programs has been developed. In short, the motivating concept for the CPRC seems to be valid, practical, and worthy of export to other interested users.

A number of practical considerations, coupled with plans for increased CPRC usage, argue persuasively for CPRC independence. One CPRC will be fully dedicated to planned activities in the Coronary Care Unit where a

number of demanding intervention trials will proceed. Another new project will use a CPRC in the operating room and SICU to study nifedipine protection of the ischemic myocardium during open-heart surgery. Most persuasive of all is the fact that the original reasons for SICU dependence are no longer valid. Emerging mass-storage devices are considerably more practical and provide adequate storage for the anticipated applications. To free the CPRC from dependence on the host computer for display generation a direct interface between the CPRC processor and a stand-alone version of the computer-driven video display system now used in the SICU is being designed. Existing graphic and alphanumeric modules now in the spares inventory will be utilized in conjunction with a proposed serial ASCII interface. This approach allows the stand-alone display system to be compatible with any device having a serial ASCII interface, including the TI-980 in the current CPRC configuration. The alternative of designing a parallel interface specific to the TI-980 requires approximately the same level of effort, but does not have the same benefit of long term flexibility.

In addition to redesigning the existing Clinical Physiologic Research Cart to render it independent of the SICU system, considerable thought has been given to the configuration of an advanced Clinical Physiologic Research System (CPRS) in order to more expeditiously meet a broader range of needs.

The clinical research needs to be addressed by the advanced CPRS can be conveniently divided into two categories. The first is represented by those which utilize existing signal conditioners, processing algorithms, and display formats. One example of such a research need is the nifedipine clinical trial. The second category of need is characterized by the development and evaluation of experimental clinical physiologic measurement subsystems (cardiac output subsystem, gas flowmeter), loop closing protocols (pulsatile perfusion, drug titration, blood infusion), and experimental physiologic signal-processing algorithms. Common to both these categories is the requirement for an interactive user protocol for structuring the application-dependent software. Programs would be written in separately assembled modules of code, which would be linked together and run in the CPRS employing a higher-level-language driver.

Similarly, the hardware design would stress modular components which can be easily reconfigured. When possible it would be most reasonable to utilize commercially supplied instrumentation modules. The hardware modules would be interconnected via a general purpose interface bus such as defined in IEEE Standard Digital Interface for Programmable Instrumentation (STD 488-1975).

C-4. Pulsatile Perfusion System

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The CPRC (C-3) is being used in pulsatile-perfusion studies in collaboration with the Division of Cardiothoracic Surgery. In these studies, the speed and timing of the perfusion pumping are controlled algorithmically to deliver pulsatile flow synchronized to the computer-detected QRS complexes with stroke volume adjusted on-line to satisfy the user-specified mean flow. ECG synchronization has been used rarely in the evaluation of pulsatile perfusion. The adaptive control of stroke volume has not been tried by others even though it is necessary to maintain a stable mean flow when ECG synchronization is used.

Work on the pulsatile perfusion system has included testing, evaluation, development of software safeguards, and additions of new hardware components. Before installing the system at the Surgical Research Laboratory in Wohl Hospital, a venous pump was added to complete the extra-corporeal circuit. After the pulsatile perfusion system was installed at Wohl Hospital and connected via cable to the Cardiothoracic Surgical Intensive Care Monitoring System in Barnes Hospital, the system was tested and its performance evaluated. A stepper motor with improved torque-speed characteristics was installed to provide adequate torque to drive the roller pump for any required flow rate.

The software remains the basic CPRC software with additions to externally control the speed, volume, and duration of the arterial pump. Safeguards recently added include implementation of an "emergency off" key on the keyboard, and the ability to sense, via the digital inputs, when the supply of blood is inadequate to continue pumping and to cease pumping automatically. The problems included in changing and adding to the pump software, once the system had been installed at Wohl Hospital, have demonstrated a lack of flexibility in the CPRC support and led, in part, to its recent reevaluation and proposed redesign. However, despite these problems, the entire pulsatile perfusion system is functioning satisfactorily and experimentation has begun with animal subjects.

C-5. Automated Perfusion System

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The membrane oxygenator has become the oxygenator of choice for prolonged cardiopulmonary support. Furthermore, studies have demonstrated the superiority of membrane oxygenators over bubble oxygenators even for routine cardiopulmonary bypass. The advantages of a more physiologic method of oxygenating blood have encouraged an increasing number of cardiovascular surgical teams to experiment with the membrane oxygenator. The blood circuit for a conventional membrane system contains a number of undesirable features associated with its use, including difficulty in priming the system, the need for manual synchronization of the venous and arterial pumps, and inability to shut down the system quickly after inadvertent occlusion of the venous return. The result is a high degree of stress for the perfusionist operating the system.

This automated perfusion system[1] was designed to overcome the above drawbacks. Work during the past year has moved from trials in the animal laboratory to clinical evaluation in the operating room. To date, the system has been used for thirty difficult cardiovascular surgical cases selected on the basis of anticipated times of perfusion support in excess of three hours. The reliability of the system has been outstanding. There have been no mishaps and the simplicity of the automated perfusion system makes the membrane oxygenator useable on a daily basis.

[1] R. E. Clark, T. B. Ferguson, R. W. Hagen, P. S. Berger, and C. S. Weldon, "Experimental and Clinical Use of an Automated Perfusion System and a Membrane Oxygenator," Circulation, vol. 50, no. 2, pp. II-213-II-218, August 1974.

C-6. Infant Perfusion System

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Support: RR 00396
HS 00074
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The purpose of the Infant Perfusion System is to provide those infants suffering from respiratory distress syndrome with prolonged pulmonary support through the use of an extra-corporeal blood oxygenation system. During the past year, tests on puppies, using the previously designed system (PR 12, C-10), revealed the system's inability to deal with the pressure control of the venous pump.

Two solutions to this problem are being pursued. The first approach requires that a new venous pump having more suitable pressure-flow characteristics be obtained. A market survey has been completed, and a commercial pump with appropriate characteristics has been identified. The second solution requires periodic interruptions in the venous pumping in order to determine the volume of venous return blood available for oxygenation. This approach would use the CPRC (C-3) to control the extra-corporeal perfusion system automatically. Both approaches will be explored during the forthcoming year.

C-7. West Pavilion Planning

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Support: RR 00396

Construction has begun on the West Pavilion which will be a substantial addition to the Washington University Medical Center. When completed in 1980 this addition will contain the following patient areas: intensive care units (cardiothoracic, surgical, respiratory, general medical, and burn); operating rooms (cardiothoracic, plastic, pediatric, general, urology, and orthopedic); and others (transplant service, acute dialysis, and recovery areas). The physiologic monitoring of critically ill patients in these areas has been addressed by the West Pavilion Monitoring Committee. The BCL has participated in the definition of the patient monitoring needs in this facility through staff appointment to this committee.

The Monitoring Committee has considered patient monitoring in the West Pavilion from a systems perspective, rather than as a collection of isolated monitoring devices. The goal of this approach is, of course, to achieve a system performance that transcends the performance of its individual elements. The systems perspective has influenced the committee's decisions as illustrated by the proposed establishment of a centralized monitoring service which will distribute a library of hardware modules throughout the facility on an as-required basis, rather than equipping each care area to handle maximum patient loading. In addition, a questionnaire was prepared and distributed to clinical personnel and the responses were used as an aid in preparing a preliminary monitoring system specification and a budgetary estimate.

The questionnaire responses reflect an enthusiastic local appreciation for the continuous physiologic monitoring that is available in the Surgical Intensive Care Unit. The BCL has engaged in numerous discussions with commercial concerns in order to keep up to date on commercial developments, as well as to share the useful concepts and signal-processing algorithms demonstrated in the SICU patient monitoring system. We plan to continue to work with interested manufacturers to discuss further carefully identified clinical monitoring needs along with interpretation, through our own experience, of their implications for human engineering, design strategies, and both hardware and software architectures.

C-8. Intensive Care Unit Planning - Jewish Hospital

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Support: RR 00396
Jewish Hospital

A combined Medical Intensive Care and Coronary Care Unit within Jewish Hospital is being planned and will open in 1978. During the past year, BCL staff has advised the Physicians Intensive Care Unit Computer Committee in their deliberations regarding patient monitoring in this new facility. The invitation to take part in these deliberations resulted from an appreciation by the Committee for the style of monitoring available in the Surgical Intensive Care Unit Monitoring System (C-1).

The Committee has developed a Request for Proposal which defines the performance specifications for a commercially available intensive care unit monitoring system. These specifications outline a system which has the capacity to do hemodynamic, respiratory, and fluid input/output monitoring, as well as acquire, display, and perform arrhythmia detection on the ECG signals for all twenty-two patient beds in the facility. All parameters derived from the physiologic signals will be sampled frequently and stored for 24 hours, after which they will be condensed for long term retrieval.

A mass spectrometer will be interfaced to the monitoring system for access to respiratory gas information. In addition, the system will permit specialized computations to be performed. The desire to interface this monitoring system to a Hospital Information System has been frustrated because this capability is currently beyond the state-of-the-art for commercial systems.

C-9. ECG Telemetry System for Cardiothoracic Surgery

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Support: RR 00396
Barnes Hospital

A commercially available ECG telemetry system was installed in the Cardiovascular Surgical Service of Barnes Hospital during the past year. This four patient system is used to provide centralized ECG monitoring for the following patient categories: pre-op patients known to have arrhythmic episodes, post pacemaker-implant patients, and post cardiac-surgical patients after release from the Surgical Intensive Care Unit. Many of the monitored patients are ambulatory.

The most significant problem encountered in using the telemetry system was marginal reception and excessive interference. Confirmed sources of interference were electrosurgical units in an adjacent surgical suite and malfunctioning fluorescent lights. The original antenna network was replaced and the reception and interference problems have diminished to the extent that the telemetry system is now being expanded to monitor eight patients. A microprocessor-based (A-6) version of ARGUS has been interfaced to this telemetry system, and a clinical evaluation will begin soon.

C-10. Ultrasonic Gas-Flow Instrument

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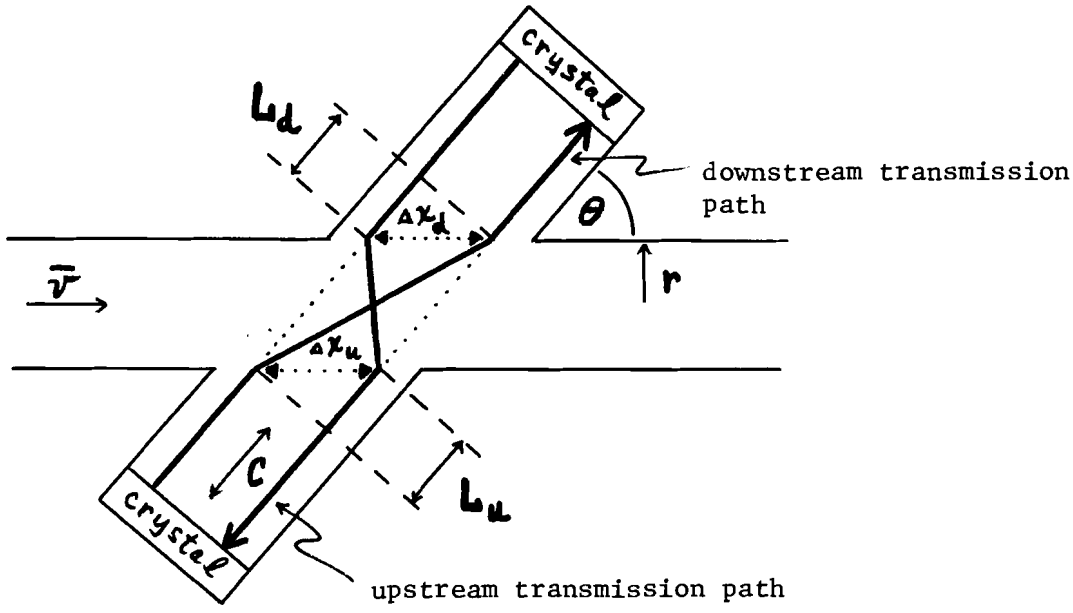
Numerous methods have been employed to measure the flow of respiratory gases in clinical intensive care units and operating rooms. This flow infor-

mation is used to evaluate the physiologic status of the critically ill patient, as well as to monitor the integrity of the peripheral mechanical respiratory circuit. Ideally, the ultrasonic method of transducing respiratory gas-flow eliminates the multiple problems associated with the presence of mechanical projections in the gas stream. Several years ago BCL purchased one of the first commercially available ultrasonic spirometers for evaluation and use with the Surgical Intensive Care Unit Monitoring System. This unit proved to be so unstable that it was not useable in the clinical environment. The local need for a suitable gas-flow instrument remained and, therefore, an effort to design such an instrument was initiated. The result of this effort is a prototype unit with precision and stability suitable for clinical purposes. During the past year this unit has been applied numerous times in the Surgical Intensive Care Unit. However, the weight and size of the transducer limits the clinical acceptance of this prototype. These undesirable characteristics can be significantly reduced by mechanical redesign.

A careful analytic evaluation has begun which will enable one to specify instrument component tolerances. Analytic evaluation consists of developing mathematical expressions for the sources of error and testing these expressions for their validity.

The gas-flow transducer has a single path two-channel geometry which is illustrated in the following figure.



Ultrasonic Gas-Flow Transducer Geometry

For the hypothetical transmission paths diagrammed in the figure, the difference between upstream and downstream transmission times, $\Delta\tau$, can be represented by

$$\Delta\tau = \frac{4r\bar{v}}{C^2 \tan\theta} \qquad (1)$$

where r is the radius of the fluid-flow path, $\bar{v}$ is the mean velocity across the flow path in the plane of the transmission paths, C is the free-space velocity of sound in the fluid, and θ is the angle between the fluid-flow and ultra-sound transmission axes. Equation (1) derives simply from the fact that the transmission path is displaced during passage of the sound energy through the flowing fluid such that the downstream and upstream transmission times are correspondingly shortened and lengthened by L_d/C and L_u/C respectively compared to the zero-flow condition. If the geometry is symmetrical then

$$L_d = L_u \text{ so that } \Delta\tau = 2L/C. \qquad (2)$$

The time required for the sound to cross the flow path is independent of v, but its course is determined by the vector sum of C and v so that

$$\Delta_x = \frac{2}{C \sin\theta} \int_0^r v(r)dr \qquad (3)$$

assuming a symmetrical flow-profile for the fluid. By defining

$$\bar{v}r = \int_0^r v(r)dr$$

equation (3) can be simplified to

$$\Delta_x = \frac{2\,\bar{v}r}{C \sin\theta} \qquad (4)$$

Note also that $L = \Delta_x \cos\theta$ (5)

so that equation (1) results from substituting equations (4) and (5) into (2).

The electronics package produces an output voltage, V, proportional to $\Delta\tau$ which is then related to fluid velocity by

$$V = k\Delta\tau = \frac{4kr\bar{v}}{C^2 \tan\theta} \qquad (6)$$

or, by rearranging,

$$\bar{v} = \frac{VC^2 \tan\theta}{4kr} = \frac{\Delta\tau C^2 \tan\theta}{4r} \qquad (7)$$

The importance of each of the four variables on the accuracy of $\bar{v}$ can be examined by simply taking the partial derivative of $\bar{v}$ with respect to $\Delta\tau$, C, θ, and r.

$$d\bar{v} = \frac{\delta\bar{v}}{\delta\Delta\tau}\, d\Delta\tau + \frac{\delta\bar{v}}{\delta C}\, dC + \frac{\delta\bar{v}}{\delta\theta}\, d\theta + \frac{\delta\bar{v}}{\delta r}\, dr$$

The following table shows the values of the derivatives at $\bar{v}$ = 0, 2, and 10 m/sec.

Derivatives and Units	Effect of Changes in Variables on $\bar{v}$ Estimation		
	$\bar{v}$ = 0 m/sec	$\bar{v}$ = 2 m/sec	$\bar{v}$ = 10 m/sec
$\delta\bar{v}/\delta\Delta\tau$, (m/sec)/μsec	3.50	3.50	3.50
$\delta\bar{v}/\delta C$, (m/sec)/(m/sec)	0	.0116	.0580
$\delta\bar{v}/\delta\theta$, (m/sec)/rad	0	4	20
$\delta\bar{v}/\delta r$, (m/sec)/mm	0	-235	-1177

Assumed nominal values are C = 345 m/sec, $\theta = \pi/4$ rad, and r = 8.5 mm. Two and ten m/sec are typical peak velocities which might be encountered during quiet breathing and during a moderately vigorous inspiratory effort through a tube with an 8.5 mm radius.

At low flow rates the errors involved in determining $\Delta\tau$ are clearly the most important, while estimation errors in geometry and in the speed of sound dominate at high flows. With these error sources in mind, we have begun a detailed evaluation of the electronic circuitry to determine the effects of internal noise and non-linearity on estimates of flow. This approach allows complete separation of the inaccuracies inherent in the signal processing from those generated in the acoustic path.

Preliminary results indicate that the delay-to-voltage conversion circuit contributes approximately 1% uncertainty (standard deviation of slope over full operating range), but this is increased by a factor of three when the acoustic signal amplifiers are included in the measurement. When the evaluation data for the electronic package are complete these will be compared with the total system performance data (using controlled gas-flow) to determine which portion of the system needs redesign so that the instrument can be replicated.

C-11. Thermodilution Cardiac Output Studies

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Support: RR 00396
HS 00074

The automated evaluation of circulatory status, as well as cardiac function over extended periods, is not now practical. Such a capability would be valuable for critically ill patients in a labile state or where studies require careful definition of ventricular function curves during volume loading. More or less continuous direct-Fick methods are fraught with practical instrumentation limitations, especially if a high inspired-oxygen concentration is being administered. Repeated injections for dye-dilution result in a progressively rising background concentration. Conventional thermodilution has been automated, but requires substantial equipment for the maintenance and delivery of the ice-cold injectate bolus. Attempts to use room-temperature injectate have not been successful, especially when a respirator is used. We have chosen to address the problem of using room-temperature injectate because of its greater convenience and its feasibility where a digital computer is available to control the injection and to evaluate and process the resultant thermal signals.

An instrumentation system has been developed which requires no bridge balancing or corrections for nonlinearity over a $10^{o}C$ range. Error analysis had revealed that non-linearities inherent in thermistors and bridge circuits without compensation could generate errors in cardiac output as high as 17%. The temperature-sensing instrumentation is in use in the animal laboratory where a digital data acquisition system is used to collect simultaneous temperature and instantaneous blood flow data (via electromagnetic flow meter) in the pulmonary trunk or aorta in open chested dogs. Early results confirm that "physiologic noise", as well as periodic variations in real blood flow, are significant, especially in open-chested animals ventilated by intermittent positive pressure. Clinical experience with the use of a commercially available thermodilution cardiac output system leads one to suspect that respiratory "artifact" is not unique to open-chested dogs.

An apparently significant observation is that the expression we have derived for the cardiac-output calculation on the basis of thermodynamic considerations differs from that conventionally employed. Comparison of the two expressions in a simulation shows that the conventional expression will give consistently higher values for flow. In fact, the difference accounts almost exactly for that demonstrated by Sorenson, et al,[1] in their very careful comparison with dye dilution. The two expressions in question are given below.

CONVENTIONAL:

$$F = \frac{V_i K(T_b - T_i)}{\int_{t=0}^{\infty}\left[T_b - T_m(t)\right] dt}$$

THERMODYNAMICALLY DERIVED:

$$F = \frac{K\, V_i}{\int_{t=0}^{\infty} \frac{T_b - T_m(t)}{T_m(t) - T_i}\, dt}$$

ρ = density,
s = specific heat,
F = flow,
V = volume,
T = temperature,
t = time,
i = indicator,
b = blood,
m = mixture of i and b, and
$K = \rho_i s_i / (\rho_b s_b)$.

Several dog experiments were performed in order to determine which expression is most appropriate to the Swan-Ganz catheter technique. Instantaneous pulmonary blood flow and temperature were recorded simultaneously. The calculated blood flows were compared with the integrated instantaneous flow value, as measured by an electromagnetic flowmeter. The second expression produced a significantly smaller zero offset than the first expression. Furthermore, when the indicator volume, V_i, was back calculated using the digitized instantaneous flow and temperature data, the use of the thermodynamically derived expression resulted in a calculated indicator volume that was much more independent of blood flow than was the case for the conventional equation. Therefore, the evidence to date shows that the second expression will improve the accuracy of the cardiac output calculation when bolus injections of thermal indicator are used. The experiments frequently show disturbingly large differences between the electromagnetic flowmeter measurement and the flow as calculated by using a bolus injection of thermal indicator. These discrepancies are particularly troublesome when the goal is to automate the measurement and apply it clinically to patients on respirators. The errors inherent in the calculation of average flow, using the bolus injection of thermal indicator, are discussed by Cropp, et al,[2] and have certainly been apparent in our animal experiments. Several experiments have been completed in order to evaluate the feasibility of using the constant infusion method for measuring cardiac output during conditions of variable flow. Contrary to popular belief there is a significant thermal "recirculation" effect in anesthetized dogs. A number of strategies are being examined to circumvent this problem.

(1) M. B. Sorensen, N. E. Bille-Brahe, H. C. Engell, "Cardiac Output Measurement by Thermal Dilution: Reproducibility and Comparison with the Dye-Dilution Technique," Annals of Surgery, vol. 183, pp. 67-72, 1976.

(2) G. J. A. Cropp, and A. C. Burton, "Theoretical Considerations and Model Experiments on the Validity of Indicator Dilution Methods for Measurement of Variable Flow," Circulation Research, vol. 18, pp. 26-48, 1966.

D. Databases for Disease Management and Research

The need for database facilities in several BCL projects became compelling in the early 1970s. The quantity and diversity of data for these projects had grown unmanageable by manual methods. Prior experience underscored the desirability of interactive data entry in order to assure adequate quality and to provide easy access to up-to-date information. Primarily through external funding, a minicomputer-based system (MUMPS) capable of supporting database activities was imported, rewritten for the PC-1200, and applied in radiation oncology. Over the intervening years this application has developed into a flourishing installation located within the Mallinckrodt Institute of Radiology. A fee-for-service installation, the Medical Computing Facilities, was organized within the Medical School to provide MUMPS service to those who do not desire to operate their own installation. BCL, itself, has continued to operate a MUMPS facility for training purposes and investigation into database characteristics.

Current activity of the lab includes the development and operation of several information systems for the support of ongoing research projects and routine clinical practice. Almost all of these databases concentrate on chronic diseases because of the importance of a long-term database to clinical investigators working with long-standing illnesses. Our enthusiasm for MUMPS has continued and efforts over the past few years have been in support of the national MUMPS Users' Group's (MUG) objective to become self-sufficient and independent of major governmental funding. The standardization of MUMPS and the subsequent commitment of major vendors to the support of that standard has provided promising opportunities for application program transfer and has given added impetus to research in new methods for the development of medical applications packages.

Following a long-standing tradition of the laboratory, an increasing emphasis has been placed on allocating the appropriate computer resource to each information processing task. As the databases which are described in this section mature, their analyses become of increasing importance. Because of the richness of the software development and because of the overall suitability of a general-purpose large-scale computer for analysis tasks, they have been performed largely on the University's IBM System/360. SAS, a popular statistical analysis/data management package, has provided the primary vehicle for the analysis of databases managed on other computing systems.

Experiences with disparate applications and with the instrumentation of conventional information systems continue to benefit design activities. Development activities directed toward a high-performance information system capable of smooth growth have been federated within the Information Systems Group, a sister Resource group based in the Computer Science Department.

D-1. Glaucoma Center Registries

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EY 00336
HS 00074

In 1974 investigators in the Glaucoma Center initiated automation of their records to facilitate clinical research. From BCL's interest in characterizing clinical databases and their usage[1] a collaborative effort emerged. Rather than design a new information system, MISAR[2] was imported (PR 12, D-15). Since then the registries have grown and their supporting programs have been improved.[3] The registries have facilitated both clinical[4,5,6] and database research.[1,7,8] Utilization of the registry has increased and it is estimated that 75 to 80 percent of the Glaucoma Center's charts are included, half of which are represented by a complete summary of encounters. An indication of growth is given by the following summary:

	June 1976	July 1977
Records	640	1272
Characters	360,000	1,510,000
Avg. no. of characters per record	560	1190

Several studies have demonstrated the clinical utility of the registry. The computerized records of 110 normal subjects were used to complete the data required for an analysis of visual field changes in ocular hypertension.[5] Subjects on the "advanced field loss" and "split fixation" lists were selected to support a recent thesis on the visual prognosis in advanced glaucoma.[6]

A study of the biological activity of glucocorticoids on fibroblasts from patients with open-angle glaucoma and normal controls with NN corticosteroid responses required matching on the basis of age, race, sex, and diagnosis. Out of the approximately 1200 subject records examined, a list of 20 matched pairs was produced by a combination of computer and manual searching. Ten of these pairs were found to be suitable for the necessary skin biopsies. Equivalent manual searching would have been prohibitively tedious.

In another study the records of those Glaucoma Center subjects who had previously participated in a protocol to test the efficacy of topical

progesterone in blocking increased intraocular pressure due to dexamethasone were retrieved and re-evaluated.

A further example of the clinical utility of this computer system was the ability of the staff to easily find an age-, sex-, and race-matched group of subjects with secondary glaucoma to serve as controls for a group of subjects with primary open-angle glaucoma. A further condition for inclusion in the study was that all subjects previously had tonography while receiving epinephrine therapy.(4)

A significant activity of this reported period was the transfer of data on 37 parameters from each of 663 records for a statistical analysis of the relationships between HLA type, diabetes mellitus, and glaucoma (D-19). A reevaluation of the data already entered into the registry, a selection of new data items to be added, and their entry and checking, along with the creation of MUMPS routines to facilitate the transfer, made this analysis possible. Additional BCL computer resources (I-15) provided a quick error-free transfer of data from MUMPS' LINC tape to an IBM/360 SAS compatible format.

(1) R. H. Greenfield, "Characteristics of Clinical Data Base Files and Their Usage," D.Sc. dissertation, Washington University Sever Institute of Technology, St. Louis, Missouri, December 1976; also available as BCL Monograph No. 303.

(2) R. H. S. Karpinski and H. L. Bleich, "MISAR: A Miniature Information Storage and Retrieval System," Computers and Biomedical Research, vol. 4, no. 6, pp. 655-660, December 1971.

(3) R. H. Greenfield, M. A. Kass, and J. P. Livingston, "A Computerized Glaucoma Data Base," Archives of Ophthalmology, vol. 95, no. 8, pp. 1365-1367, August 1977.

(4) B. Becker, S. W. Montgomery, M. A. Kass, and D. H. Shin, "Increased Ocular and Systemic Responsiveness to Epinephrine in Primary Open-Angle Glaucoma," Archives of Ophthalmology, vol. 95, no. 5, pp. 789-790, May 1977.

(5) W. M. Hart, Jr., and B. Becker, "Visual Field Changes in Ocular Hypertension: A Computer Based Analysis," Archives of Ophthalmology, vol. 95, no. 7, pp. 1176-1179, July 1977.

(6) A. E. Kolker, "Visual Prognosis in Advanced Glaucoma," Transactions of the American Ophthalmological Society, in press.

(7) R. H. Greenfield, "Clinical Data Base Usage," presented at the Third Illinois Conference on Medical Information Systems, Chicago, Illinois, November 1976, proceedings in press.

(8) R. H. Greenfield, "Requirements for an Ophthalmologic Data Base," Proceedings of the Digital Equipment Computer Users' Society, vol. 3, no. 4, pp. 1393-1397, Spring 1977.

D-2. MIPI (Myocardial Infarction Patient Information) Database

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The MIPI system (PR 12, A-1) continues to manage the three data gathering phases associated with the Sudden Death study: 1) the recording of all CCU admissions for Barnes and Jewish hospital patients and the gathering of relevant clinical data for all MI cases, 2) the scheduling of Holter recordings and the acquisition of various data elements, and 3) the follow-up done on all surviving MI patients. Over the past year

the system has stabilized, with most software changes being made to support the follow-up phase of the project and for changes made to data forms already defined in the system. One addition still to be made to the system is the transfer of data to tapes so they can be placed in a SAS database (D-17). Since the conversion of the system from DEC-11 to standard MUMPS is finally complete, the data transfer problem can now be tackled.

All patients admitted to the Barnes CCU or Jewish MICU are noted in the system via entry of a Registry Enrollment form. When this registration of admission is made, a tracking record is established, which allows the system to control entry of all following data items, relate the status of any particular file, and generate lists of files requiring specified data items. Depending upon the admitting and final diagnoses, the system then requires and controls the entry of subsets of the fifteen forms which make up the in-hospital phase of the study. Although the admission, CCU diagnosis, CCU discharge, and hospital discharge or death of each CCU-admitted patient is documented in the system and, in addition, risk factor and onset of symptom data are collected on all patients with rule-out MIs or MIs, the major emphasis of the data collection procedures revolves around patients diagnosed as definite MIs. The CCU stays of these patients are documented with data concerning physical findings, arrhythmias, clinical laboratory values, ECG findings, and, where applicable, hemodynamic parameters and/or CPK values. In addition, an attempt is made to recruit these patients into the Holter monitoring program if they survive their CCU stay.

For patients recruited into the Holter monitoring program 2 recordings are made, the first 10-14 days post-MI and another 2-3 months post-MI, and then, for those patients determined by the system to meet eligibility criteria for continuation in the study, the recordings are continued at three month intervals. The MIPI system notes patients to be scheduled and generates all correspondence related to the recording. As each recording is made, a tracking record is established so the system can control all of the diverse sources of data relating to the recording: 1) forms completed at the time of recording, 2) the digitization and Argus/H edit of the tape (A-4), 3) the cardiologic review of the Argus/H edit results, 4) serial reading of the 12-lead ECG taken at the time of recording, 5) successful passage of cycle-save data to the IBM System/360 and subsequent recycling of digital tapes, and 6) data collected for a special lipid research project. As with the in-hospital phase of the system, the tracking record for each recording allows a system user to determine the status of different aspects of the Holter recording phase of the project.

All surviving MI patients are periodically followed to determine their post-MI status. The system takes care of generating letters for the first contact which is made through the patient's private physician. Further contact is made with the patient either by phone or computer generated letter. For patients who have expired, all available data surrounding the circumstances of the death are gathered (one source being a computer generated questionnaire sent to the physician) in order

that a blinded summary of the data can be made and then coded independently by four project personnel. The system notes discrepancies in coding for later resolution through a group meeting.

Presently the volume of data stored in the MIPI system can be summarized as follows:

	Barnes	Jewish
Patients Admitted	1960	1851
Diagnosis of Definite MI	470	343
Holtered Patients	164	150
Holter Recordings Made	348	328

The MIPI system has aided project personnel in the collection of quality data in a consistent fashion. Because the system guides its users through a relatively complex protocol, it cuts down on the number of data items missing or in error because of omissions made during various data collection procedures.

D-3. PIM (Protection of Ischemic Myocardium) Database

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Support: N01 HZ 62960
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The original Myocardial Infarction Patient Information (MIPI) system (D-2) was generalized and upgraded to produce the PIM system which is used to coordinate a double blind propranolol intervention study run by St. Louis University and two collaborating institutions, St. John's Mercy Medical Center and Veteran's Administration Hospital. Data are collected concerning the hospital and especially the CCU stay of any patient admitted to one of the three participating CCUs to rule out an MI. The selection of forms completed concerning the patient's stay is determined according to the classification of the patient's case: 1) recruited for study, 2) eligible but not recruited, 3) not eligible but MI was diagnosed, and 4) not eligible and no diagnosis of MI. The patient is noted in the PIM system via entry of the CCU Admission form and the classification of the patient is determined from two other forms completed and entered for all patients, Study Admission and CCU Discharge. As in the MIPI system, the PIM system manages and controls the entry of all data forms once the patient is entered into the system.

Presently the PIM system revolves around the collection of data on forty different forms, most of which are used only for patients recruited into the drug intervention study. For all patients, data are collected to document risk factors and ECG changes and to describe the onset of symptoms. In addition, for MI patients, the course of the patient's CCU stay is recorded via data concerning physical findings and arrhythmias and data concerning the hospital discharge or death. For eligible non-recruited patients the above mentioned forms are completed, along with forms concerning a 12-lead ECG taken 10-14 days post-MI, chest x-rays, and the minimum and maximum of certain lab values taken during the CCU stay.

For recruited patients the number of forms completed rises sharply. Besides the data mentioned above, hemodynamic measurements are made for 72 hours, metabolic measurements for 6 days, propranolol blood levels for 10 days, and CPK measurements for a maximum of 126 hours. Thallium, pyrophosphate, and HSA scans are made at various scheduled intervals during the hospital stay and 6 Holter recordings are also taken. All medications administered during the first 14 days of the hospital stay are recorded with a computer code number and dosage, and any significant event during this time is also noted by time of occurrence via an elaborate coding system. These events are coded in one of nine classifications: 1) subjective patient complaints, 2) clinically significant events, 3) arrhythmias coded by frequency, 4) arrhythmias coded by duration, 5) conditions warranting drug stoppage, 6) protocol steps not performed, 7) procedures performed, 8) ambulatory report, and 9) miscellaneous.

Presently the in-hospital phase of this system is complete and has been converted from DEC-11 to standard MUMPS. As in the MIPI system, data are edited at the time of keyboard entry so errors are flagged immediately. Also, as forms are entered a tracking record is maintained, which controls the entry of all data. Using this tracking record the status of any file can be checked and lists generated of "things-to-do". One enhancement to the information system for the PIM study has been the ability to run a batch program which performs those special tracking and editing tasks at night not requiring operator intervention. Any files needing special attention are saved until time is available for inspection by the data entry clerk. This feature allows data to be edited by comparing responses made on different forms.

Future enhancement of the system includes development of software support for the follow-up phase of the program. Recruited patients are scheduled for follow-up visits at 3, 6, and 12 months post-MI, at which time five procedures are done, stress test, thallium and HSA scans, ECG, Holter recording, and chest x-ray, and a follow-up form is completed. Also, another addition to the system will be the passage of data to a SAS database (D-17) for statistical analysis.

At this time, there are 654 patients registered in the PIM system. Of these 193 are documented MIs and 40 met the entrance criteria for the propranolol intervention study. So far 29 patients have been recruited into the study.

D-4. SCOR Patient Information Database

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Support: RR 00396
HL 17646

A system of general purpose programs was written for the SCOR Interdata computer (PR 12, A-12; A-19) to facilitate the entry of discrete SCOR patient data into a computer database. Data records are entered into the Interdata, then written on the magnetic tape which is transported to the IBM System/360 where the permanent SAS database (D-17) is maintained. About 350 patients have now been entered into the file and follow-up records have been obtained for a large number of them.

We first utilized this database to examine the relationship between enzymatic estimates of infarct size and mortality. Results of this study showed that infarct size discriminates between survivors and nonsurvivors only when patients with a history of previous myocardial infarction and elderly patients are excluded. Future studies will concentrate on exploring the correlation between infarct size and exercise capacity and ejection fraction measured at the time of follow-up examination. Additional studies already completed concern effects of selected therapeutic agents on enzymatically estimated infarct size and prognosis have been reviewed elsewhere. (1-7)

(1) B. E. Sobel, "Prediction and Limitation of Infarct Size," Proceedings of the European Symposium on Myocardial Infarction, Turnberry, Scotland, pp. 11-20, October 1976.

(2) R. Roberts and B. E. Sobel, "Creatine Kinase Isoenzymes in the Assessment of Heart Disease," American Heart Journal, in press.

(3) M. S. Klein, P. A. Ludbrook, J. W. Mimbs, F. H. Gafford, T. A. Gillespie, C. S. Weldon, B. E. Sobel, and R. Roberts, "Perioperative Mortality Rate in Patients with Unstable Angina Selected by Exclusion of Myocardial Infarction," Journal of Thoracic and Cardiovascular Surgery, vol. 73, pp. 253-257, 1977.

(4) T. A. Gillespie, H. D. Ambos, B. E. Sobel, and R. Roberts, "Effects of Dobutamine in Patients with Acute Myocardial Infarction," American Journal of Cardiology, vol. 39, pp. 588-594, 1977.

(5) R. E. Coleman, M. S. Klein, S. A. Ahmed, E. S. Weiss, W. M. Buchholz, and B. E. Sobel, "Mechanisms Contributing to Myocardial Accumulation of Technetium-99m Stannous Pyrophosphate after Coronary Arterial Occlusion," American Journal of Cardiology, vol. 39, pp. 55-59, 1977.

(6) M. S. Klein, R. E. Coleman, C. S. Weldon, B. E. Sobel, and R. Roberts, "Concordance of Electrocardiographic and Scintigraphic Criteria of Myocardial Injury after Cardiac Surgery," Journal of Thoracic and Cardiovascular Surgery, vol. 71, pp. 934-937, 1976.

(7) K. S. Gowda, T. A. Gillespie, H. D. Ambos, B. E. Sobel, and R. Roberts, "Effects of External Counterpulsation on Enzymatically Estimated Infarct Size and Ventricular Dysrhythmia," British Heart Journal, in press.

D-5. Neonatal Database

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Support: RR 00396
Missouri Division of Health, Special Project Grant

A busy Neonatal Intensive Care Unit (NICU), such as the one at St. Louis Children's Hospital, can easily become mired in the sheer volume of patient data generated during extended hospitalizations (29-day average locally). Furthermore, the need for careful retrospective and prospective clinical research in Neonatology is critical since so little is presently known about most of the disease processes affecting the newborn infant. During the past two years, we have developed a computerized database (PR 12, D-16) to assist Neonatologists in conducting meaningful clinical research.

The MUMPS-based system operates on the Artronix PC-12 system at the Mallinckrodt Institute of Radiology. Data entry and retrieval at the NICU utilize a CRT data terminal with telecommunications to the remotely located system. User acceptance of the system has been extremely good. During an initial 18 month period of system operation, admission data on over 800 patients were collected and methods for collection and compression of voluminous free-text in-hospital data were developed and refined.

Interaction with members of the Department of Neonatology in order to establish clinical research needs, combined with a systematic

review of the successes and failures of other similar systems, has resulted in the system being designed around three basic criteria:

1) The system should have the capability to search rapidly through a large number of patient files for the existence of multiple, simultaneous, user-specified criteria.

2) Interaction with the system for searching the data should be by physicians, not by programmers. Search routines should have simple question and answer formats and physicians should have enough understanding of the internal data structures to be able to query the system for data that are both clinically relevant and within the purview of the system. Obviously, the burden of understanding placed on the physician should not discourage usage of the system.

3) The system should respond to the needs of the clinical researcher. In particular, the system should not represent an attempt to develop a real-time, patient-care oriented system.

The first criterion was satisfied by adopting the technique of collecting free-text medical data, encoding it via dynamically generated "coding catalogs", and then storing the encoded data in two types of files, a "general" patient file, and a series of inverted files to be accessed during database searches. The inverted files are generated by use of the technique of bit mapping which enables users to search the database of nearly 1000 patients with response times of less than one minute. Encoded data are collected during two separate encounters. First, the Admission History and Physical (H/P) is obtained upon a patient's admission to the NICU and then reviewed and encoded by a medical student (average time, 7 min/chart). Second, data for an In-Hospital Summary sheet are generated by physician review of each patient's complete medical record using a Problem/Concurrent Event/Complication approach (average time, 35 min/chart). The validity of the encoding strategy was carefully checked in several sessions in which previously encoded medical records were recoded for comparison. Both H/P and In-Hospital data encounters showed acceptable reproducibility rates (>90%).

The second criterion (ease of physician interaction) was implemented by mirroring external and internal file structures. Externally, coding catalogs were structured hierarchically using a logical textual format familiar to physicians. Internally, this hierarchical structure was reserved via multi-level subscripted data nodes. To search the database, the physician-user merely responds to a series of prompts. The entered characters correspond to the numbered entries in the hierarchical coding catalogs from which multi-level bit map subscripts are derived. In addition, the In-Hospital Coding Catalog contains a series of bi-directional pointers which allow physicians to search for subsets of patients with varying degrees of disease-occurrence generality (e.g. "Patients with acidosis as a complication of hyaline membrane disease," or "Patients with acidosis accompanying any pulmonary process," or only "Patients with acidosis").

The third design criterion (applicability to clinical research) was addressed by allowing the entry of quantitative data for a variety of laboratory tests on patients selected by a user for close study. Lab data are internally ordered by time and available for both graphic and tabular printouts, thus facilitating the identification of trends that might otherwise remain obscure.

Plans to begin new collections of both H/P and In-Hospital data on all NICU patients are in the final stages. Several clinical studies based on retrospective analysis of existing H/P data are also planned. Software improvement continues and looks toward the incorporation of various statistical analysis packages. In addition, transfer of the software to the new Artronix PC-16 based MUMPS system will provide additional bit-function features which should decrease search times.

D-6. Computerization of Cardiology Tests/Reports at Jewish Hospital

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A pilot project is underway to computerize the generation of various reports sent to private physicians concerning cardiac evaluation tests performed at Jewish Hospital. At the present time these reports of the interpretation of the tests are typed from forms completed by medical personnel. The goals of the system to be developed are twofold: 1) to increase the efficiency of the cardiology office by decreasing the amount of time required to produce each report, and 2) to stimulate research with the data which will now be in computer readable form.

In the eventual system the patient will be registered into the computer system when his first contact with the cardiology office is made. At that time identifying patient information will be recorded, along with next-of-kin and medical insurance data. As each test is performed the patient's last name and date of birth will be used as the key to add all relevant data to the patient's file. This strategy was picked, rather than the use of some identifying number, in order to eliminate the need to determine a patient's reference number prior to data entry. After all data for a particular day have been entered those results which should yield a printed report to the personal physician will be noted and then generated at a convenient time (usually after regular office hours). The generated report will include the physician's

name and address so no manual lookup of this information will be required. It should be noted that the data entry personnel and not the system will assume responsibility for the generation of reports since the volume of data is relatively small. Eventually the system will be enhanced to allow searches of the data, pulling off subsets of data for statistical analysis, and storage of data on devices other than disk.

At the present time only the exercise test has been computerized. Although the groundwork for the echocardiogram test has been done, minor software changes are needed to include this test in the system. The initial reactions of the secretaries to using a computer terminal rather than a typewriter have been favorable and there are now 90 patient files stored in the system.

D-7. Database for Pilot Study on Barnes' CCU Patients with Chest Pain

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A temporary database of patients admitted to the Barnes CCU between October, 1974, and January, 1977, was established to determine if a relationship exists between ECG data, the MB CK isoenzyme determinations, and 99mTc pyrophosphate scintigrams. The patient population consisted of all patients admitted with a chief complaint of chest pain: i.e. angina, rule-out or definite myocardial infarction (MI), pulmonary edema, or embolus. Information in this database is the result of a merging of data recorded in the MIPI database (D-2) with the additional keyboard entry of needed data not found in that system. The data items recorded are relatively few: name, admission date and diagnosis, length of CCU stay, final CCU diagnosis, serial 12-lead ECG data including T-wave changes and presence or absence of Q-waves, myocardial scan data, and MB CK data.

The database consists of the following:

	MI	non-MI	TOTAL
Number of patients	674	1059	1733
MI Scans Done	327	305	632
MB CKs Run	638	941	1579

At present the results are still being analyzed in order to determine whether similar data should be collected in an ongoing fashion.

D-8. A Research Bibliography System

Personnel: R. H. Greenfield, BCL

Support: RR 00396
HS 00074

The bibliography system created to serve the reference needs of the study of clinical database files and their usage (PR 12, D-8; D-15) has remained a useful tool. It greatly facilitated the preparation of that study's bibliography (72 citations). The system now contains in excess of 700 citations on computerized information systems in medicine (especially ophthalmologic uses of computers), database/information retrieval, and several other assorted and related topics.

The system is oriented towards maintaining lists of, and indices to, journal articles. These citation lists and indices are very useful in the office, in the library while doing research, and in organizing a subset of a personal bibliography while writing a paper. In addition to the accession, author, reference, and source indices and mixed-case listings, rapid on-line searches of articles by author can be made. These searches utilize phonetic (Davidson and Soundex) techniques to reduce sensitivity to incorrect spelling of author names. The utility of these phonetic techniques is addressed by the studies outlined in D-15. A monograph incorporating a users' guide and programmers' reference has been prepared.(1) The documentation and the code have been described in a MUMPS Users' Group (MUG) "MUMPS Abstract" (D-11) and are available upon request. This system is also described in the literature.(2)

(1) R. H. Greenfield, "A Bibliography System," BCL Monograph No. 311, February 1977.

(2) R. H. Greenfield, "A Unique On-Line/Off-Line Bibliographic System," to be presented at the 1977 MUMPS Users' Group Meeting, September 1977, proceedings to be published.

D-9. MUG Publication and Plans Towards Self-Sufficiency

Personnel: J. Zimmerman, BCL
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Support: RR 00396
HS 01540
Pauline Sterne Wolf Memorial Home Fund, the Baylor College of Medicine, Department of Surgery
The MITRE Corporation

In the last 12 months the mailing list for the MUMPS Users' Group (MUG) has almost doubled and now includes over 4200 people from around the world. There are 600 to 700 institutions that use MUMPS, mostly for medical applications. MUG has enjoyed federal funding for 4 years, during which time it has developed substantial income from a variety of sources, all of which contribute to the probable long-term self-sufficiency of the group. There were several other sources of income for MUG. Institutional MUG memberships raised $4,000, while individual memberships produced $3,500. Attendance at the 1976 MUG Meeting brought $4,000, attendance at the associated workshops and tutorials produced $2,000. while fees for vendors' booths brought $750. These and several minor sources raised the total income for that year to over $18,000 ($4,000 due to documents), a slight increase over the approximately $14,000 obtained in the previous fiscal year.

Many MUG publications were released in the last year.[1-10] Monthly income on orders for these documents has now grown to about $300, with about 60 documents being ordered each month. In addition, about $150 income results monthly from sales of two MUMPS Development Committee (MDC) publications, Programmer's Reference Manual[11] and Documentation Manual[12] (about 30 copies of these documents are purchased monthly). Sales of MUG documents, including annual meeting proceedings and others in addition to those listed above, resulted in a total income of about $3,000 for June, 1976, through May, 1977. Sales increased strongly in the last few months because new titles were added to those available, and these and previous titles were publicized in several press releases. Sales of MDC documents totaled about $1,400 for the same period. The income from these documents is used for duplicating, mailing, and secretarial costs.

MUG Treasurer, Donald Glaeser, estimated that a minimum annual income of $22,700, exclusive of income from documents, was needed to allow MUG to become self-supporting. To increase income membership

fees were tripled and a membership drive was started.[13] Registration fees for the annual MUG Meeting were increased and the number of workshops for which people paid an additional fee was doubled from two to four.

Parallel with such tactics to increase income from membership fees, meeting and workshop attendance, and document sales, publicity of MUG was extended through frequent press releases. The most successful release concerned the Standard MUMPS Pocket Guide resulted in well over 1000 queries for information on MUMPS. MUG publicized MUMPS at many national conferences, including the semi-annual DECUS Symposia, the triennial MEDINFO Congress, the annual National Computer Conference, and the annual meeting of the Society for Computer Medicine.

It is felt that the growth in the number of MUMPS users and of international awareness of MUMPS combine to make it possible for MUG to derive its necessary minimum income from its sales. Thus MUG, built upon the strong base provided by federal funding, has developed into an independent information resource for medical computing.

(1) J. Zimmerman, compiler, Book of MUMPS, MUMPS Users' Group, St. Louis, Missouri, 1977.

(2) J. Zimmerman, ed., MUMPS News, MUMPS Users' Group, St. Louis, Missouri, # 18-21, 1976-1977.

(3) F. R. Sias, Jr., compiler, Proceedings of the 1976 Southeastern Region MUMPS Users' Group Meeting, MUMPS Users' Group, St. Louis, Missouri, 1976.

(4) J. Zimmerman, compiler, 1977 MUMPS Institution Profiles, MUMPS Users' Group, St. Louis, Missouri, 1977.

(5) J. Zimmerman, compiler, 1977 MUMPS Application Abstracts, MUMPS Users' Group, St. Louis, Missouri, 1977.

(6) R. F. Beckley and D. A. Bridger, Advanced MUMPS Techniques, MUMPS Users' Group, St. Louis, Missouri, 1977.

(7) D. G. Robida, COMAPS, A Computer-Aided Pharmacy System, MUMPS Users' Group, St. Louis, Missouri, 1976.

(8) H. A. Elder and T. Munnecke, LUMPS (Loma Linda University MUMPS Programming System) Design Manual, MUMPS Users' Group, St. Louis, Missouri, 1976.

(9) C. F. Peth, G. G. Edick and N. W. Hickman, MUMPS Application Design Manual for a Hospital Admitting System, MUMPS Users' Group, St. Louis, Missouri, 1976.

(10) F. R. Sias, A Survey of MUMPS Billing and Accounting Applications, MUMPS Users' Group, St. Louis, Missouri, 1977.

(11) M. E. Conway and P. L. Egerman, Programmer's Reference Manual, MUMPS Development Committee, St. Louis, Missouri, 1976.

(12) L. J. Peck and R. A. Greenes, MUMPS Documentation Manual, MUMPS Development Committee, St. Louis, Missouri, 1976.

(13) J. Zimmerman, ed., MUMPS News, # 19, November 1976 and # 20, February 1977.

D-10. MUMPS Application for the MUG Application Library (MUGAL)

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Several applications implemented earlier (PR 12, D-19) in the MUMPS-PC dialect have been translated into Standard MUMPS. They include the questionnaire driver ("QUEST") and the documentation package ("DOC"). Both of these applications have been expanded and improved after translation. A Standard MUMPS teaching program was written using the QUEST driver, a utilities package has been started, and a simple statistics package has been expanded.

QUEST and the Standard MUMPS program have been transferred to 14 institutions around the world:

1. Albany Medical Center, USA.
2. Case Western Reserve University, USA.
3. Free University of the Netherlands and MUG-Europe, Amsterdam, Netherlands.
4. George Washington University, USA.
5. Goethe University, Frankfurt, Germany.
6. Hoskyns, United Kingdom.
7. Kettering Medical Center, USA.
8. Lister Hill Center, National Institutes of Health, USA.
9. MUG-Japan.
10. University of California, Davis, USA.

11. University of Pennsylvania, USA.
12. University of Washington, USA.
13. Washington University School of Medicine, Department of Surgery, USA.
14. West Midlands Health Authority, United Kingdom.

The teaching program introduces MUMPS concepts, commands, functions, and operators. A student's performance is evaluated on the basis of whether he is re-asked a frame or question (implying that he answered it or some subsequent frame incorrectly) and how long he takes to respond to a frame. For a novice programmer taking three different lessons (concepts, commands, and functions), between 10% and 30% of the frames were re-asked and the mean response time ranged from 30 to 70 seconds. Percentages of repeated frames and mean response times both decreased when the programmer repeated lessons, showing that material had been learned. For an experienced MUMPS programmer taking the same lessons about 10% of the frames were re-asked, primarily because of carelessness on the part of the programmer, and mean response time was only 10 seconds.

The documentation package (DOC) facilitates the semi-automated production of documentation that meets most requirements of the MUMPS Users' Group and the MUMPS Development Committee. The main part of DOC is an automatic cross-referencer, which identifies local, global, and system variables, routines and lines referenced, command types, function types, instances of indirection, and other features of MUMPS code. About half of DOC's capabilities reformat automatically the data from the cross-referencer as requested. The other capabilities allow the documenter to enter, edit, and print text comments. DOC has been transferred to the University of California at Davis, and will be transferred elsewhere upon completion.

Design Manuals for each of the applications are being prepared and revised to meet the specifications described in PR 12, D-19.

D-11. MUG Application Library (MUGAL) Experiences/Plans

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The idea of a program library was germinal in MUMPS standardization.(1) MUGAL is intended to be a centralized repository and distributor of machine-readable code, though to date it has been limited primarily

to publication of an index and abstracts to direct MUG members to the authors of programs for further inquiry.

To estimate the potential usefulness of MUGAL, studies were performed which confirmed the difficulty of transferring large applications, but concluded that MUGAL could, for smaller programs, reduce many of the transfer problems that had been experienced. These problems included:

- Lack of awareness of transferable programs,
- Lack of responsiveness from the originators,
- Lack of management-level summaries,
- Lack of technical documentation,
- Incompatible file structures,
- Dialect differences,
- Cryptic I/O messages,
- Site-specific features.

MUGAL would have more incentive than the originators to promote solutions.(2)

MUG is attempting to learn from and interact with other users' groups. Possible interfaces with other languages are being investigated.(3) A survey of 14 other software libraries, in both government and private industry, has been conducted to help MUGAL plan its technical emphasis, operations, and funding. Among the many relevant findings are:

- Small utility and system programs far outnumber application programs (such as business, engineering, or medicine).

- Standards for programs and documentation vary tremendously, with most libraries not screening rigorously.

- A hypothetical "median group" has 764 members, has a library of 505 programs, grows at about 40 programs/year, distributes about 1000 programs/year, and is operated by about two full-time equivalent persons.

- Libraries with large application programs tend to be government-affiliated and supported by subsidies; total self-sustenance from membership and program orders appears difficult.

- Problems for users center around poor documentation and site-specificity, similar to MUMPS transfers.

MUG is unusual in that it is organized around a language rather than a single subject area or manufacturer, yet it can benefit from the experiences of other groups.

Criteria for programs to be included in MUGAL have been established(1) and are more comprehensive than those of most other libraries. Several packages are complete and have been distributed (D-10).

There has been debate concerning the degree of technical involvement that MUGAL can afford since MUG dues cover only operations at about the current level of activity (D-9). Increased staffing and finances would be required if MUGAL were to engage in documentation or evaluation of submitted programs, or in extensive creation of new programs. Further research has been proposed to determine the cost-effectiveness of MUMPS code transfer. The resulting data would help to define the optimal policy for MUGAL.

(1) A. W. Forrey, "The MUG Application Library," in Book of MUMPS, MUMPS Users' Group, 1977.

(2) D. K. Tao and J. Zimmerman, "MUMPS Application Exchange," Proceedings of the Digital Equipment Users Society, vol. 3, p. 2, USA, Fall 1976.

(3) A. W. Forrey, "Utilization Committee Activities and Progress of MUGAL," MUMPS News, # 21, MUMPS Users' Group, May 1977.

D-12. MESCH

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The Multi-Environment Scheme (MESCH) project recognizes the institutional differences among ambulatory-care groups and the difficulties these differences cause in the development and transfer of automated ambulatory-care record systems (PR 11, D-15; PR 12, D-12). MESCH provides a capability for each group to specify its own needs by means of an interactive questionnaire, and to have its customized information system developed.

Previous surveys of the differences in uses made of medical-record data have been expanded with regard to data collected in registration and encounter forms, data contained in medical records, and the needs that physicians have when they use the data.[1,3] New surveys have identified the uses made of automation in group practices in St. Louis and of the automated services provided by vendors for the physician's office (D-13). Those surveys have enabled us, during the last year, to plan the contents and structure of the questionnaire to be used for the specification of data to be manipulated. Preliminary development of the MESCH questionnaire for such areas as patient identification of the frame or question types that will occur most frequently are:[2]

- Yes/No frames, for which the user responds to the question with either a "Yes" or "No". This occurred in 40% of the frames.

- Answerless frames, in which explanatory material is presented but no question is asked. This occurred in 16% of the frames.

- Single selection from a menu of choices, in which the user denotes one particular answer from a displayed list of alternatives. This occurred in 15% of the frames.

The remaining 29% of the frames included questions that requested an answer within a particular numeric range, and questions where a menu of answers was presented but more than one answer could be selected.

It is planned that when the questionnaire is developed it will be used by a team of physicians, administrators, and others representing a particular care group. Techniques have been investigated for converting the user's specifications into a working system. These techniques include conditional compilation and the building of code around kernels.

[1] J. Zimmerman and R. K. Stimac, Survey of Registration and Encounter Forms, BCL Monograph No. 321, in preparation.

[2] J. Zimmerman, "Towards Generalized Automated Ambulatory-Care Record Systems," MEDINFO 77, Proceedings of the Second World Conference on Medical Informatics, Toronto, pp. 473-478, August 8-12, 1977.

[3] J. Zimmerman, Preliminary Study of Physician Utilization of Medical Records, BCL Monograph No. 297, August 1976.

D-13. Automation in the Physician's Office

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In conjunction with the MESCH project on ambulatory-care record systems (PR 11, D-15; PR 12, D-12; D-12), three research projects have been conducted:

- a survey of St. Louis group practice,
- a proposed systematic methodology by which a group may decide whether automation is its most appropriate alternative,
- a survey of financial and clinical information systems offered by vendors.

Seventy-six group practices were identified in a telephone survey. In size distribution and degree of specialization they are very similar to a national profile compiled by the American Medical Association.(1) The percentage using computers (about 60%) is also very close to the national average (56%) reported by the Medical Group Management Association,(2) although St. Louis has more utilization of service bureaus and less of in-house computers. A second more detailed survey of all groups using computers is now near completion. It investigates specific applications implemented or planned, factors influencing the initial decision to automate; the processes of specification, development, and implementation, and problems and benefits.

A guide for physicians or administrators considering automation for a group practice is being prepared. It defines the systems approach to decision making, outlines the financial, administrative, and medical applications that might be implemented; suggests a methodology to weigh the costs and benefits of automated solutions; and illustrates the systems approach with three case studies from St. Louis group practices.

To evaluate MESCH against other choices, one needs an awareness of the breadth and depth of vendor involvement in health-care computing. Over 200 vendors have been identified. However, the number was condensed to about 170 which are still active in marketing medical applications (not just hardware). A response rate of 85% was achieved prior to final follow-up. About half the vendors emphasized the hospital setting and about half the office setting, with only a few companies serving both. In some major application areas the percent of vendors offering a product was: billing/accounting and management reporting, 80%; ancillary services

(lab, pharmacy, radiology), 60%; medical records (including history, order entry, summaries, abstracts, etc.), 50%; scheduling, 30%; admitting, 24%; inventory, 15%. For billing/accounts receivable, 56 functions or reports, described by over 100 terms, were identified by analyzing 16 vendors who supplied details on their capabilities. Similar analyses will be done for other application areas. Special attention will be given to the scope of variations and amount of flexibility and customization offered. Two conclusions are already apparent:

- The number of nonfinancial medical applications for the physician's office is small. Most advanced efforts occur in hospitals. However, many companies plan to add applications in scheduling, medical records, and ancillary services in the near future.

- The great variety of functions and reports in billing/accounts receivable may be suitable for a modular approach. Since the typical vendor offers only about 20 options (out of 56) a MESCH-like system that allows free selection might be very attractive.

(1) C. Todd and M. E. McNamara, Medical Groups in the US, 1969, AMA, Chicago, 1971.

(2) R. Engleman, "Computer Service: Tool for Better Practicing," Group Practice, pp. 13-25, September-October, 1975.

D-14. Demonstration Health Information System

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A basic medical information system was developed as a collaborative project between Health Care Technology (HCT) and Health Care Administration (HCA) graduate students. The primary goal of the project was to provide HCT and HCA students with experiences in the specification, implementation, and acceptance testing of various modules of an automated medical information system.

The information system was divided into six parts, or modules, covering major medical, financial, and administrative functions that would be needed in a hospital. These modules were:

1. Patient registration, identification, and room assignment.

2. Entry of medical record data.

3. Patient billing and accounting and related fiscal reports.

4. Internal budgeting between revenue centers (labs, radiology, etc.) and cost centers (clinics, medical record room, etc.).

5. Medical reporting, including a discharge summary for the patient's hospitalization, lab tests, and other profiles.

6. Administrative reporting, including number of admissions, length of stay, and bed occupancy.

For each of these six modules a team was established, three HCT students and one HCA student. The team members worked together in designing, implementing, and testing their module. The resulting six modules formed an integrated information system. The students reported that their practical experience with this project was very educational, and at least one attributed the job offers he received to his work on this information system.

D-15. Characteristics of Clinical Database Files and Their Usage

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Studies on five characteristics of computer databases in a clinical environment have been successfully concluded since last reported (PR 12, D-8). The objective of these studies was to highlight for the designer of clinical database systems a number of the special problems posed by this very demanding environment. The five topics (length of data items, indexing methods, database aggregates and their size and growth, temporal relationships, and database usage) were chosen because of their almost universal presence and because details pertaining to them often were omitted from initial designs.

Data for these studies were obtained from four active data systems: a research bibliography system, the Glaucoma Center Registries, the

Medical Care Group Information System, and the Mallinckrodt Institute of Radiology Diagnostic Computer Facility Information System. These systems are described in detail in the prepared report.[1] The research bibliography system (D-8) and the Glaucoma Center Registries (D-1) remain available to conduct future studies of this nature. In fact, the Glaucoma Center Registries continue to gather monitoring data on registry size and growth and on system usage. In addition to the overall report of these studies,[1] several publications and oral presentations were prepared.[2,3,4]

[1] R. H. Greenfield, "Characteristics of Clinical Data Base Files and Their Usage," D.Sc. dissertation. Washington University Sever Institute of Technology, St. Louis, December 1976; also available as BCL Monograph No. 303, December 1976.

[2] R. H. Greenfield, "Clinical Data Base Usage," presented at the Third Illinois Conference on Medical Information Systems, Chicago, Illinois, November 1976, proceedings in press.

[3] R. H. Greenfield, "Requirements for an Ophthalmologic Data Base," Proceedings of the Digital Equipment Computer Users' Society, vol. 3, no. 4, pp. 1393-1397, Spring 1977.

[4] R. H. Greenfield, "An Experiment to Measure the Performance of Phonetic Key Compression Retrieval Schemes," Methods of Information in Medicine, in press.

D-16. Measurement of MUMPS Buffer Pool Operating Characteristics

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The concept of a simple, relatively inexpensive, single-user MUMPS system, which could be utilized either as an independent "MUMPS machine" or as part of a network, motivated this study. The principal determinant of both cost and performance in such a system was expected to be the mass storage system used for MUMPS global and program storage. Preliminary calculations showed that currently available flexible disk drives, while appropriately low in cost, would not provide adequate performance. Some type of hierarchical storage organization, using a comparatively small amount of higher-speed storage as a buffer or

cache for a flexible disk, thus seemed indicated. The "buffer pool" scheme used in some current MUMPS systems is, in effect, such a hierarchical mass storage organization. The work reported here involved the measurement of characteristics of a buffer pool operation in a production MUMPS environment.

The system on which these measurements were made is a DEC PDP-11/40 with MUMPS-II Version 4 used for support of the Barnes Hospital Clinical Microbiology Laboratories. A database of over 7×10^6 bytes was maintained, containing all microbiology requisitions and results for a 45-day period, plus extensive statistics used for quality control and infectious disease reporting. Several independent research databases were also maintained. At the time of this study the system supported seven terminals, three of which were used in the Clinical Microbiology Laboratory, and processed 200 to 300 specimens per day.

Data on buffer pool operation were obtained by inserting additional code into the MUMPS operating system global routines to collect statistics on the number of global references, number of continuation blocks accessed, and on the frequency of actual physical disk reads. These measurements were made on several different days of the week, as well as during different periods through the day, in order to obtain some idea of the variation in measured parameters under differing types of system loads. In addition, a separate set of measurements was made to determine the buffer pool "hit rate", which is the percentage of time that a requested disk block was found in the buffer pool and no physical disk read was necessary. These hit rate measurements were made not only under different operating conditions, but also with two different buffer pool sizes.

The results supported some simple predictions. For example, the buffer pool hit rate decreased markedly with more than one heavily disk-bound user. With a single user, and with a buffer pool of 32 blocks, the measured hit rate was as high as 30% for some applications programs. These results are heavily dependent upon the particular MUMPS implementation used and, in particular, upon its buffer pool management strategy. Data collected with such an "instrumented" MUMPS system (including disk access traces) could, however, assist in the development of improved buffer management algorithms.

D-17. SAS As an IBM System/360 Data Management Tool

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The utilization of minicomputers under MUMPS as an environment for the interactive data acquisition and the management of the information-gathering process has been quite successful for a number of studies in the management of chronic diseases (D-1, D-2, D-3, D-4).[1,3] However, for analytic tasks requiring the processing of large groups of patients, the application of more computationally burdensome statistical procedures, or the production of large reports, the general-purpose IBM System/360 has provided a more appropriate environment.[4,5]

Because of its strong data management components, SAS 76[6] has been chosen as the chief tool for the analysis of databases gathered with these other computer systems. The relevant data management facilities of SAS may be broken down into five general categories:

1) input flexibility,

2) self documentation,

3) storage management,

4) rearrangement of data,

5) support of traditional data processing activities.

In addition to supporting traditional keypunch preparation of data, SAS supports a large variety of internal (binary) input formats facilitating the reading of industry-compatible tapes on the IBM System/360, which were prepared on other computer systems. Industry-compatible tape has been the primary mode for interfacing the IBM System/360 to the data collection computers, including the MCF machine (D-2, D-3), the SCOR computer system (A-19, D-4), and the MUMPS PC System (D-1, D-19, I-17), the latter through the use of the newly developed nine-track tape interface (I-15). SAS's support of a free-format, list-directed

input, in which data items are delimited by blanks, has facilitated the task of tape-generation in MUMPS and provided a significant degree of data reduction.

SAS allows for each variable to have associated with it a label which is in turn utilized in the output from the statistical and reporting procedures and a format code to govern the display of data values. In addition, for each data set, SAS retains a history of the files and SAS program statements utilized in the creation of that file for the preceding n generations. In many cases the variable labels and formats can be automatically extracted from the data entry prompts on the MUMPS machine and transferred directly to SAS.

Data sets are organized by SAS in libraries residing in a single OS data set on either disk or tape. The user has control of the precision (and thus, storage space) allocated for each variable. By providing the necessary tools for the listing, creation and deletion of data sets within a SAS library, SAS removes from the user much of the administrative burden associated with database management on a large IBM System/360.

SAS facilities for rearranging records within a data set or merging information across data sets are clearly superior to other statistical/data management systems. Easy merging of information from separate data sets facilitates studies in which there are a multiple of pathways by which the data become available to the SAS system as well as providing a friendly environment for a multiple-form data collection strategy, as used in the MIPI and PIM studies (D-2, D-3). A common problem in the analysis of longitudinal data results from the fact that for some analyses one may wish to treat each encounter with the patient as a separate observation, while for others, the patient and all of his encounters become the unit of analysis. Other analyses are to be performed on subsets of the data or are applied to each subset. Often it is necessary to compute derived measures as functions of the original data. All of these operations are facilitated by the programming statements available in SAS.

In support of the analysis and data cleaning operations it is often desirable to produce selected lists of the database or subsets thereof for further examination. These lists, either in a quick and dirty, or in a more stylized report form, are exemplary of the traditional data processing operations performed on the database with the resulting printed and/or microfiche reports produced for subsequent review. Easily accessible archival data storage, file updating operations, (in either old master/new master or isolated data value forms) are also often desired.

In addition to the data management facilities described above, SAS provides a full complement of standard statistical analysis routines commonly utilized for the subsequent analysis of clinical data. The general linear model procedures (analysis of variance, analysis of covariance, multiple regression) represent state of the art techniques for the analysis of the unbalanced data sets normally encountered in

clinical research. The range of SAS capabilities is also extended by: 1) the combining of procedures currently available (e.g. transforming variables to their rank values and then executing standard statistical procedures to allow nonparametric tests to be performed); 2) the supporting of a powerful matrix manipulation language allowing new techniques to be quickly implemented; and 3) allowing the user to add new statistical procedures to the system and distributing user contributed procedures. All three of these techniques are utilized in methodological developments described elsewhere (D-18).

(1) J. Achtenberg, J. P. Miller, P. Cryer, and J. Santiago, "Data 3 -- A Form Management System," Proceedings of the 1976 MUMPS Users' Group Meeting, in press.

(2) P. Moore, J. P. Miller, K. W. Clark, G. C. Oliver and M. Moran, "A Management Information System Designed to Oversee a Clinical Study," Proceedings of the 1976 MUMPS Users' Group Meeting, in press.

(3) J. Achtenberg and J. P. Miller, "Diabetes Center Patient Registry," Proceedings of the 1975 MUMPS Users' Group Meeting, Washington, D.C., pp. 1-7, September 17-19, 1975.

(4) K. W. Clark, P. Moore, J. P. Miller and L. J. Thomas, Jr., "A Total Systems Approach to the Quantitative Analysis of Holter Recorded ECGs," accepted for presentation at the International Symposium for Ambulatory Monitoring, London, England, September 1977.

(5) J. P. Miller, P. Moore, J. Achtenberg and L. J. Thomas, Jr., "Computer Resource Allocation for Long-Term Clinical Studies," accepted for presentation at the IEEE Conference on Computers in Cardiology, Rotterdam, September 1977.

(6) A. J. Barr, J. H. Goodnight, J. P. Sall and J. T. Helwig, A User's Guide to SAS 76, SAS Institute, Raleigh, North Carolina, 1976.

D-18. Methodological and Technical Developments for Risk Function Analysis

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A frequent problem in the analysis of data obtained on chronic diseases is to estimate a mathematical function which will allow the estimation of the probability of some future event, such as death, given a vector of data for a patient. Generally, data are available on the vector of observations and subsequent presence or absence of the predicted event for a group of patients. Risk function analysis may be performed for several distinct, but overlapping, purposes. First, to empirically identify individuals with increased risk who may then be exposed to treatments or observations whose cost or risk may be justified only in the presence of an increased risk of morbidity or mortality. These high-risk patients may also be utilized for evaluations of interventions. Second, by identifying which variables contribute to the ability to predict a future event, it may be possible to more clearly elucidate the potential mechanisms of the subsequent event, thus providing clues for potential intervention strategies. Finally, risk function analysis would allow the evaluation of the independence of a risk marker or observed intervention in predicting subsequent morbidity or mortality.

There are four general statistical models which are commonly utilized for risk function analysis. Linear discriminate analysis (LDA) is probably the most familiar. Under the assumptions of the vector of observed variable being distributed multivariate normally, a simple linear combination of the vector of observations is obtained and a posterior probability of group membership may be estimated. An additional assumption of linear discriminate analysis is that the variance-covariance matrices of the vector of variables are equal between the groups subsequently experiencing the event and those not experiencing the event. By relaxing this latter assumption, but retaining the multivariate normality assumption, a solution which is quadratic in the Xs (QDA) may be obtained. The posterior probabilities obtained as a solution from LDA or QDA are in the form of the multivariate logistic, i.e. $P = \frac{1}{1 + \exp(\alpha + \beta X)}$. By applying an iterative technique, maximum likelihood estimates of α and β can be estimated, thus relaxing the distributional assumptions for the Xs, but retaining the functional form of the probability estimation model. In previous studies of cardiovascular disease which have compared these maximum likelihood estimates with the posterior probabilities

obtained from LDA[1,2] it has been observed that either procedure appears to work well for the identification of variables contributing to the prediction, but that the agreement between the predicted and observed probabilities was closer for the maximum likelihood estimated probability. Since LDA is computationally much less expensive, if the purpose of the risk function analysis is simply elucidating those variables contributing to the prediction, LDA appears to be preferable. However, the maximum likelihood estimators appear to be preferable for purposes 1) and 3).

A fourth model involves the identification of subgroups of the patients who are homogenous with respect to the risk of the subsequent event. While some algorithmic approaches are available a clinically enlightened repetitive subgrouping, as advocated by Feinstein,[3] appears to be the technique most widely utilized. Unfortunately, there are no statistical techniques known to be able to estimate the statistical reliability of subgroups identified in this manner from the sample on which the subgrouping was originally derived.

Since none of the widely available statistical packages provide a procedure for the maximum likelihood estimation of the multivariate logistic, a procedure was initially implemented using PROC MATRIX of SAS. After developing the details of the iterative technique and validating its potential usefulness a new statistical procedure (PROC PREDICT) was implemented. PREDICT utilizes the solution from an LDA as initial values and rapidly converges to the maximum likelihood estimates of the parameters. By utilizing the matrix of second partial derivatives of the estimates of the parameters as estimates of the asymptotic variance-covariance matrix of the parameters may be made, thus facilitating confidence intervals on α and β.

Because of the assumptions of multivariate normality necessary for LDA and QDA, applied statisticians have often utilized transformations of the original observed variables utilizing simple mathematical functions, with the resulting variables more nearly approximating the normality distributional assumptions. Often the choice of a transformation was made by choosing from among those available in a laundry list of such transformations available in a particular statistical package. Since the choice of the particular transformation was quite arbitrary and a more unified approach was needed, a new technique for selecting the functional transformation was developed. No single family of functions suffices for all transformations, but a set of three functions originally described by Johnson[4] can be shown to be sufficient. By utilizing normal scores obtained from the order statistics and nonlinear regression techniques an appropriate transformation may be chosen. The technique may be adapted to obtain the equality of variance in each group for LDA or the later constraint may be relaxed for QDA. The technique has been implemented within SAS and has been described in detail elsewhere.[5,6]

While recent advances have been made in the estimation of error rates for LDA by the application of jack-knife techniques, the best method of estimating the adequacy and accuracy of a particular statistical model is the validation of the estimation procedure in a separate replication sample. For the study of sudden death we have been evaluating first the alternative statistical models by examining the ability of various attributes observed during the acute phase of the myocardial infarction to predict subsequent in-hospital death. The database of some 1150 patients admitted to the Barnes and Jewish CCUs with the confirmed diagnoses of myocardial infarction has begun. We are applying each of the statistical models to the subset of patients admitted to Barnes Hospital CCU, and will then test the solutions obtained on the Jewish Hospital sample. Following our evaluation of the alternative models we will turn next to the prediction of sudden death within one year following the MI among those patients who survive their hospitalization. The sample utilized for the development of the risk functions will be those patients who were enrolled into the Holter monitoring study, and the resultant solution will be validated on patients who have survived their MI but were not enrolled into the study. Again, a comparison of the alternative statistical models can then be performed.

(1) S. H. Walker and D. B. Duncan, "Estimation of the Probability of an Event as a Function of Several Independent Variables," Biometrika, vol. 54, pp. 176-179, 1967.

(2) M. Halperin, W. C. Blackwelder and J. I. Verter, "Estimation of the Multivariate Logistic Risk Function: A Comparison of the Discriminant Function and Maximum Likelihood Approaches," Journal of Chronic Diseases, vol. 24, pp. 125-158, 1971.

(3) A. R. Feinstein, "Clinical Biostatistics: XIV, The Purposes of Prognostic Stratification," "XV, The Process of Stratification (Part 1)," "XVI, The Process of Prognostic Stratification (Part 2)," "XVII, Synchronous Partition and Bivariate Evaluation in Predictive Stratification," Clinical Pharmacology and Therapeutics, vol. 13, pp. 285-297, pp. 442-457, pp. 609-624, pp. 755-768, 1972.

(4) N. L. Johnson, "Systems of Frequency Curves Generated by Methods of Translation," Biometrika, vol. 36, pp. 140-176, 1949.

(5) J. P. Miller, "A Parsimonious Approach to Data Transformation," Proceedings of the Second Annual SAS Users Group International Conference, SAS, Inc., Raleigh, North Carolina, pp. 74-78, 1977.

(6) J. P. Miller, "A Parsimonious Approach to Data Transformation," accepted for presentation at the 1977 Joint Statistical Meetings, Chicago, Illinois, August 1977; to be published in the Proceedings of the Statistical Computing Section of ASA.

D-19. Statistical Analysis of the Relationship of HLA and Diabetes To Glaucoma

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Previous statistical utilization of the Glaucoma Center data has been in terms of small subsets of patients with particular characteristics, who were then evaluated according to more detailed protocols (D-1). A continuing interest within the Department of Ophthalmology is the association between specific HLA haplotypes and the presence of glaucoma. Since diabetics appear to be at increased risk for glaucoma and diabetes has also been associated with specific HLA haplotypes, the study of the relationship between the two diseases and HLA was initiated.

The data entry process was accelerated so that all center patients who had been haplotyped were entered into the Registry (D-1). These data were then transferred to the IBM System/360 where the database was to be analyzed by utilizing SAS (D-17).

The data to be transferred were divided into two subgroups, one of which consisted of data items which had only a single data value per registrant, such as date of birth or sex, and the other of items with multiple occurrences, such as ocular diagnoses. All items were transmitted in a format where the data item number was followed by the data values, all data items for a particular patient being preceded by the patient's identifier, and the entire database prepared with values being separated by blanks, thus facilitating reading in the list-directed input mode of SAS (D-17). The data were written on LINC tape, transferred to another PC with a newly developed industry-compatible nine-track tape drive (I-15), and the industry-compatible tape then transmitted to the IBM System/360, where it was read by SAS to create a SAS data library. One SAS dataset was created for those variables with single values per patient and separate datasets were created for each multiple valued variable. In each dataset a patient identifier was retained so that the relevant information for specific analysis could be extracted and merged with other relevant information for subsequent analyses.

E. Cardiac Catheterization Laboratory

During the past decade, computer-assisted data acquisition and analyses have become applied routinely in many cardiac catheterization laboratories (cath labs). Over the last five years many commercially available and privately developed systems have appeared. Most cath lab systems provide on-line data acquisition, mass data storage, varying degrees of labor- and time-saving automated analyses, and report generation. Recent work at the Biomedical Computer Laboratory has built upon experience with an earlier prototype to develop an advanced cath lab system (COMCAT) which provides conventional functions but emphasizes flexibility and close integration with the clinical laboratory procedure in order to expedite data collection and analysis. Features which make the system more responsive to the user include simplicity of operation during the procedure, easy customization to other laboratories, provision for multiple patient conditions, availability of automated data-acquisition protocols, and convenient editing capabilities. Uncomplicated access to data for research applications adds to the usefulness of the system. A prototype has been tested, refined, and used clinically with enthusiastic acceptance by staff and physicians.

Development of computer-assisted left-ventricular angiographic analysis has progressed in parallel with the cath-lab computer system effort. This work is divided into two parts: 1) Computer calculation of left ventricular function parameters from manually entered ventricular contours; and 2) Digitization of flouroscopic video images and computer determination of the ventricular contour. COMVAS is a computerized ventricular-contour analysis system which, during its continuing development at Jewish Hospital, has been providing analysis and efficient archival storage for manually entered contours valuable both for research and for routine clinical diagnosis. Experiments are now in progress to establish optimum sampling strategies for real-time digitization of video images with sufficient resolution in the X, Y, and Z axes for automated ventricular-contour recognition. To this end, state-of-the-art techniques are being applied to achieve a data-acquisition rate (to disk) of 9.6 Mbytes/sec. Work on the contour-recognition algorithm builds on published reports of others and seeks to capitalize on a larger image context by employing models of left-ventricular shape.

Other activities include an on-going effort to complete the last of the pressure-waveform pattern-recognition algorithms used in the new catheterization laboratory computer system. Also, studies of left-ventricular compliance being conducted at the Washington University Catheterization Laboratory have necessitated the development of specialized off-line data-acquisition and analysis software.

E-1. Expanded Cardiac Catheterization Laboratory System

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The New Cardiac Catheterization Laboratory Computer System (COMCAT)[1] (PR 12, E-1) has been in routine clinical use for more than one year. While numerous software improvements continued to be made throughout this year, personnel at the Jewish Hospital catheterization laboratory have been critically evaluating COMCAT. Many of the novel features of COMCAT have been found to be very beneficial to the overall performance of the laboratory.

Conclusions from the clinical evaluation of some of the more important features are presented here:

1. The computer prompted acquisition and control (COMPACT) panel (PR-12, E-1) has appreciably simplified and improved computer operation when compared with the predecessor cath lab systems (PR-10, F, and PR-11, E). Functions which previously required two or three key strokes can now be accomplished by pressing a single button on the COMPACT panel. Illumination of active buttons on the panel greatly facilitates rapid and convenient evaluation of the current system status. The COMPACT panel's physical layout, as well as self illumination, makes bidirectional communication with the computer simple despite the typically low ambient lighting levels. With the panel has come a number of features that have proven valuable for data acquisition. An example is the "pullback" capability permitting the acquisition of gradient data using non-simultaneous pressures. This feature has made possible generation of significant new information without requiring any additional complexity during data acquisition.

2. The application of pre-defined procedural "protocols" has added significantly to the usefulness of the COMCAT system. The protocol concept has been well received by the Cath Lab staff and is used in nearly every case. A significant decrease in the number of catheterizations containing missing or incomplete information has resulted. The cardiac catheterization technicians note that while they almost always deviate from the protocol at least once during a catheterization it provides an underlying framework

for the procedure and enhances the continuity of the catheterization. Recent pressure-scale additions to each protocol entry have been well received also.

3. The inclusion of extensive editing capabilities in COMCAT has been exceptionally helpful. Despite the ease of COMCAT operation, operator errors during data acquisition continue to occur. The ability to retrospectively edit the data directory has been particularly useful in this respect. Approximately 95% of cardiac catheterizations require some retrospective data-directory editing. The "protocol" feature has reduced greatly the pressure on the technicians during data acquisition. For example, if a particular pressure can be sampled briefly only once, it is possible to acquire the pressure immediately without regard for specifying its attributes. Information about that pressure can be added or changed at a later time without loss of data. The overall editing capabilities incorporated in COMCAT have resulted in a substantial increase in the accuracy of data acquired and processed by the system.

4. Automated procedures for ventricular and arterial waveform analysis have been operational for approximately one year. The high degree of accuracy produced by these routines has resulted in widespread physician acceptance of the automated results. A significant feature of COMCAT, however, is its retention of a manual analysis-override capability. The automated analysis algorithms fail in certain instances of dysrhythmia. The operator is notified in each case and convenient manual analysis can be performed. As a result, no useful data are denied analysis and presentation because of unusual features. More recently, automated procedures for gradient analysis have been added and are being evaluated.

5. The COMCAT system parameter initialization feature has proven valuable in numerous situations. Not only has this capability permitted tailoring COMCAT to the specific laboratory configuration required at Jewish Hospital, but it has also accommodated changes in laboratory technique. One example is a recent change in the dye-dilution cardiac output determination methods at Jewish Hospital, which were accommodated by typing in a simple parameter change using the initialization editor.

6. The ability to perform dye calibration for the cardiac output densitometer after the catheterization has been completed has made COMCAT more compatible with standard clinical procedures. The incorporation of "dummy" calibration values has permitted the cardiologist to obtain relative comparisons of cardiac output during a catheterization without requiring calibration of the densitometer prior to the catheterization procedure.

7. Enhanced data summaries for each cardiac catheterization are generated optionally on a line printer or graphic display with hard copy, using new formats stratified by conditions and anatomic location. These summaries have been well received by the clinical staff and are incorporated routinely into the patient's chart.

8. The "user's system" providing research programmers with access to cath lab data through FORTRAN-callable subroutines has been quite useful in several research applications. Present and future applications have inspired further expansion of this provision for interacting with the cath lab software and data without knowledge of the COMCAT internal structure.

Various cath lab hardware additions (PR 12, E-1) have proven valuable. Additional improvements such as the addition of text display to the COMPACT panel are under consideration.

The cath lab hardware suffered only one minor failure in this year and COMCAT hardware and software malfunctions have been minor and few, no data having been lost due to these malfunctions.

(1) G. H. Brandenburger, B. R. Hieb, S. A. Garfield, R. J. Krone, P. A. Ludbrook, J. R. Cox, Jr., and G. C. Oliver, "A New Cardiac Catheterization Laboratory Computer System," Proceedings of the Conference on Computers in Cardiology, IEEE Catalog No. 76 CH 1160-1C, St. Louis, Missouri, pp. 343-346, October 7-9, 1976.

E-2. Automatic Ventricular Boundary Extraction from Video-Angiographic Data

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During routine x-ray cardiac angiography a large number of left ventricular (LV) images are recorded for determination of LV function indices. Normally the images are recorded on film, are developed later, LV borders are manually traced, and various LV contour parameters are calculated to assess cardiac performance. The vast amount of LV image data, the time necessary for film developing, the tedium associated with manual LV boundary tracing, and the number of cardiac performance parameters to be computed, all motivate complete automation of the cardiac angiographic analysis.

A computerized ventricular-contour analysis system (COMVAS)[1] has been developed (PR 12, E-3) and is in routine clinical use at Washington

University in the Jewish Hospital Cardiac Catheterization Laboratory. The system uses manually-traced LV contours from cine-angiographic films to automatically analyze stored sequential contours to determine regional myocardial-contractility indices.

To overcome the time limitations imposed by the cine-film preparation and developing procedures, an experimental macromodular video data acquisition system was constructed (PR 11, E-1) to assess the realizability of a real-time LV image digitization and storage. The results indicate that real-time LV image data acquisition is indeed possible with currently available high-speed A/D converter and disk storage technologies.

Finally, to eliminate the time and labor resulting from manual LV boundary tracing as well as to improve accuracy and repeatability of LV boundary identification, an automatic LV boundary extraction algorithm has been demonstrated[1] to be suitable for implementation.

Further inquiries have shown that in order to digitize and store a standard 525-line, 60 Hz, 2-to-1-interlaced 4-MHz bandwidth video signal "in real time," it is sufficient to satisfy the following system specifications: digitization of every other video field, 8-bit grey-level video signal quantization, sampling a 128-by-128 (typical) pixel array window with 100 nsec between sample points on a horizontal TV scan line, storage of an image array on a single cylinder of an industry-standard 3330 disk drive. The limiting factor to the image array size has been shown to be the disk drive serial data rate (1.2 Mbytes/sec, unformatted). However, modifications to the disk drive read-write electronics will increase the data rate (to 9.6 Mbytes/sec), thus permitting larger array sizes to be digitized. Twenty-seven seconds of video information then can be digitized "in real-time." However, due to smaller bandwidth requirements for the actual LV video signals available, an optimum sampling may require only small (32-by-32 typically) LV image arrays.

The optimum LV image data sampling requirements will be learned by analyzing the LV image data obtained by a slow-scan, off-line video digitizer. The digitizer has been built and is being tested. It operates on the principle of digitizing one point per horizontal TV line, in a column-wise fashion, and is used to digitize static video images obtained from still TV frame video sources, such as a video-tape recorder operating in "frozen frame" mode or the PEP 400R scan-converter display system (PR 11, E-4). The flexibility of this digitizer makes available choices in odd or even TV field selection, 12-bit grey-level quantization, variable digitization array-window size (256-by-256 maximum), choice in sample point separation (200 nsec horizontal, 1 horizontal line vertically, minimum), and array-window position. Initially the digitizer will be used to determine the minimum spatial and grey-level sampling required for reliable boundary extraction algorithm performance.

To aid the LV algorithm optimization a Science Accessories Corporation NT-211 graphic tablet interfaced to the PC-12 will be used to manually enter LV contours from LV images displayed on the PEP 400R display system.

In addition to its above-mentioned uses the PEP 400R display system will be used to superimpose the computer-generated or manually-entered LV contours with the original LV image for comparisons.

The steps toward developing an efficient LV boundary extraction algorithm have been proceeding in three directions. First, an exhaustive literature search has been made to find the most "reasonable" algorithm for initial implementation. The algorithm finally chosen was the one developed by the research group at the Latter Day Saints Hospital (LDS), Salt Lake City, Utah.[2] Border recognition is accomplished by locating the points maximizing a product of mutually independent LV border definition factors: a matched gradient filter, a video profile predictor, a location term, and a time sequence predictor. Each factor can be considered separately for optimization and additional factors can be added later if necessary.

Second, a more optimized approach to LV border definition applicable to a wider variety of LV image data will be sought. For example, to avoid redundant searches an LV shape-model accounting for individual LV shape varieties and a "center of gravity" model to search for maxima in LV boundary definition are being formulated.

Third, an interactive image processing system, IMSYS, has been written in FORTRAN for the PC-12 to support LV image data digitization and display hardware, to characterize LV image data, and to test and experiment with various LV recognition algorithms. It is a large, overlaid, disk-resident software system designed for image data manipulation and image processing experimentation. The salient features of IMSYS are the independence of image processing tasks from image array size and the ability to completely characterize LV images. Graphic and/or grey-level displays can be produced for 1- or 2-dimensional gradients, Laplacians, and horizontal or vertical signatures. Statistical parameters, entropies, energies, and other parameters can be calculated also for each image series. The remainder of IMSYS consists of image data storage, retrieval, manual LV contour data entry and display, and IMSYS utilities.

[1] B. R. Hieb, R. J. Krone, and G. C. Oliver, "A Computerized System for Segmental Analysis of Sequential Left Ventrical Frames," Proceedings of the Conference on Computers in Cardiology, IEEE Catalog No. 76 CH 1160-1C, St. Louis, Missouri, pp. 219-222, October 7-9, 1976.

[2] P. D. Clayton, L. D. Harris, S. R. Rumel, and H. R. Warner, "Left Ventricular Videometry," Computers and Biomedical Research, vol. 7, pp. 369-379, 1974.

E-3. Algorithm Development for Atrial and Pulmonary-Wedge Pressure Waveform Pattern Recognition

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The pressure waveforms measured during cardiac catheterization inside the left or right atrium, or with the catheter in the pulmonary-wedge position, are complicated and often ambiguous even to the trained clinician without some additional information. A simultaneously recorded ECG is typically employed by the clinician to locate the four significant waveform events during each cardiac cycle: the A wave, X trough, V wave, and Y trough. A literature search has revealed no existing atrial or pulmonary-wedge pattern recognition algorithms satisfactory for use with the new cardiac catheterization laboratory system COMCAT (E-1). All existing algorithms rely upon a "beat averaging" for noise removal, pattern recognition being applied only to the average. Development of a new algorithm for atrial and pulmonary-wedge waveform pattern recognition was, therefore, undertaken. Similar algorithms were done successfully in the past for left ventricular, aortic, and arterial pressures (PR 12, E-2), and simultaneous atrial and ventricular pressures for gradient analysis (E-1). Basic waveform timing is obtained from a QRS detection algorithm (PR 8, D-5) applied to a simultaneously digitized ECG waveform.

A database was compiled from 91 catheterization procedures. Pressure waveforms and their associated analyses were retrieved via the COMCAT "User's System" and compiled into both a "test case" of 25 atrial and 23 wedge pressures and a "training case" of 22 atrial and 21 wedge pressures. Pressures were segregated according to clinical abnormalities. Each of nine physicians manually analyzed the "test case" and "training case" using COMCAT. Empirical search "windows" relative to the R-wave of the ECG for each of the four waveform events were derived from the "training case." Algorithms to identify the precise location and associated pressure value for each of the four waveform events are being developed. Using the "training case," algorithm parameters will be adjusted later to minimize the difference between algorithm-analysis results and the averaged physician analysis results.

The final algorithm performance will be evaluated using the "test case," again comparing with results of the physicians' analyses.

COMCAT has provision for this final automated-analysis overlay and routine clinical use of the algorithm can begin as soon as testing is completed.

E-4. Left Ventricular Compliance Studies

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This project is designed to characterize and quantify left ventricular (LV) diastolic compliance in patients with ischemic heart disease and to examine the relationship between compliance and extent of ischemic injury, duration of ischemia, and degree of hemodynamic dysfunction. Techniques for quantification of compliance are being developed in the Hemodynamic Laboratory and will be extended to the Clinical Investigation Unit by utilizing noninvasive techniques for left ventricular dimensional analysis.

Although various techniques have been proposed for analysis of left ventricular dimensions most are subject to serious limitations. Therefore, we have continued to rely upon quantitative angiographic methods for dimensional analysis. Quantification of compliance requires simultaneous measurement of left ventricular pressure as well as dimensions. During the first two years of this project we have developed and refined protocols for safe and accurate measurement of both parameters during diagnostic cardiac catheterization. These include: 1) data acquisition during ECG-timed slow administration of ventriculographic contrast media (to minimize stimulation of ventricular premature beats and avoid artifactual ventricular distension due to contrast medium), 2) data acquisition with angiographic catheter-tip transducers specially designed to avoid arrhythmogenic jets when contrast medium is injected and to minimize catheter motion, 3) accurate calibration and preclusion of baseline drift in the high fidelity transducer tip catheter system, 4) standardization of respiration during ventriculography, 5) continuous recording of high-fidelity pressures on a magnetic tape system with appropriate frequency response during cineangiography, 6) characterization of the frequency response of the recording system with development of an analog method suitable for determining frequency spectra of non-repetitive signals with components in the physiological range between 0.5 Hz and

1.0 kHz. This method utilizes an analog record/playback tape, memory oscilloscope, and a spectrum analyzer. Even with high-fidelity Millar transducer recordings in patients, no frequency components were present outside the frequency band of the analog tape, 7) synchronization of ventriculographic and pressure data with respect to each other and to the simultaneously obtained ECG, the time of contrast injection, and cineangiographic frame rate. Ventricular volumes were initially determined by manual tracing of silhouettes on sequential cineventriculographic frames. We have completed development of an automated technique by which ventriculographic planimetry is performed directly on the viewing screen of a Vanguard XR-35 Projector, using a Graf/Pen 3 Sonic X-Y Coordinate digitizer permitting rapid and accurate automated computation of serial ventricular volumes. The program developed also provides for analog-to-digital conversion of left ventricular pressures at the rate of 1 kHz.

Digitized data are stored on a computer disk and subsequently correlated with synchronized volume data. Pressure and volume data are tabulated and graphed as linear and/or first order exponential functions in order to examine the characteristics of the pressure/volume relation throughout diastole with particular emphasis on the late "pre a-wave" portion of the cycle. Quantification of compliance can be determined from the slope of the exponential relationship between pressure and volume. We have developed a program providing for automatic computation of serial changes in wall thickness and left ventricular mass, permitting determination of the ventricular stress-strain relationship, a potentially more meaningful expression of diastolic compliance than one dependent only on volume. Left ventricular contractility can be assessed by using simultaneously measured peak dP/dt, while the maximum rate of relaxation can be estimated from peak negative dP/dt. Ejection-phase indices of ventricular performance are computed also.

An integrated package of computer programs and electronic equipment has been assembled to quantify compliance of the human ventricle from data acquired during cardiac catheterization. Angiograms of the LV are recorded at 60 frames per second on 35 mm film. Simultaneous LV pressure, ECG, and timing pulses from the angiogram dye injector and from the cine camera are recorded on magnetic tape. Typically, two to six seconds of relevant data are collected for each dye injection. The quantity of data, precise time alignment of volume and pressure measurements, accurate instantaneous measurements of pressure and volume, standardization of inter-patient data, and expression of the same data as a function of various parameters are all facilitated by the developed system.

Ventricular volumes and wall thicknesses are calculated by the PC-12 computer after the operator has traced the angiogram outline on paper with a rho-theta plotter or on the Vanguard XR-35 viewing screen with a Graf/Pen 3 Sonic X-Y Coordinate digitizer. In response to operator commands directing the computer to selected options, various functions relating to compliance are calculated and displayed. The system is sufficiently flexible to deal with a wide range of patient values and with the

variable manner in which the data might be collected or stored in the future. The programs developed are designed to be easily expanded and altered with additional experience and operation of the system is guided by computer displays so that no special knowledge is required of the user.

Research planned in this project will entail evaluation and selection of algorithms suitable for describing and characterizing compliance. The data from both the cine run and the mock run can be applied directly to acceptable formulas of compliance and to newly proposed formulas. Analyzing a standardized database from a large selection of patients may reveal facts not evident from manual calculations in small groups. The entire software system is designed for flexibility and ease in expansion.

Left ventricular wall thickness calculation has been added to this system and full implementation of this valuable parameter expands the power of the data analysis. The addition of the sonic tablet allows more rapid and accurate calculation of ventricular volume and wall thickness. An additional FM-reproduce amplifier makes possible the use of a second pressure channel simultaneous with the first and with all of the timing signals.

F. Laboratory Biochemistry

Current BCL activities in this area are based on a modular microcomputer system being developed to automate laboratory instrumentation. Minicomputer systems are generally used with large, complex analytical instruments, such as mass spectrometers, NMR spectrometers, and X-ray diffractometers, but they are too costly for many applications. Microcomputers are cost effective, but require a substantial support system to achieve the flexibility of minicomputers. We have chosen a DEC LSI-11 microprocessor module for these small-scale applications, since this device has a minicomputer architecture, including software compatibility with the PDP-11. A set of modules has been designed for data acquisition, keyboard input, and printed output, with others planned, including a graphic display. The modules for a particular project will be selected on the basis of the minimum necessary, plus the budgetary limitations of the collaborating investigator. A number of applications have been identified in the Department of Biochemistry, including a new, rapid and very sensitive amino acid analyzer, a scanning double-beam spectrophotometer, a stopped flow kinetic analysis system, and an enzyme assay procedure. The components designed to date are being assembled into a mobile system, which has in addition to the standard modules a terminal and two floppy disk drives for program development at the site of the application. Once the programs are running on-line, the mobile system will be moved to the next application, leaving only the necessary modules at the site.

Two laboratory applications have reached the stage of routine operation, using preliminary control circuits designed while the laboratory microcomputer system was in the planning phase. An Intel 4004 microcomputer control box, previously described, controls the timing of the solvent switch valve in the new amino acid analyzer. An unusual crystallizable lipoprotein is under study, using both peptide sequencing and X-ray crystallography to establish the stereochemical structure. Such information is needed to investigate lipid-protein interactions which are essential for the stability of biological membranes. The analyzer is also being used to determine the amino acid and amino sugar composition of a glycoprotein. In another application, a paper-tape punch interface has been built for a Cary scanning double beam spectrophotometer. Punched tape is fed into an off-line PDP-12 system for data analysis. This project is part of a study of the blood coagulation system, using mathematical modeling techniques to determine the complex interactions of the many components involved.

F-1. Microcomputer Systems for Biochemical Instrumentation

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GM 13925

As indicated in a previous report (PR-12, F-1), the goal of this project is the development of a flexible set of computer modules and systems software suitable for general use with analytical instrumentation. Typical applications include automation of control, data acquisition, and/or data processing for amino acid analyzers, gas chromatographs, spectrophotometers, and assay systems requiring variable quantities of reagent addition.

The first application selected involves a new amino acid analyzer built in Dr. Leonard Banaszak's laboratory in the Department of Biochemistry (F-2). This analyzer employs a new fluorescent reagent[1] for detecting amino acids down to the 100 picomole level, a dramatic increase in sensitivity compared with conventional analyzers. This will permit the sequencing of many proteins hitherto available in quantities too small for analysis.

In this first application, the microcomputer system will control the timing and switching of solvent valves, much as an Intel 4004 microprocessor-based controller now does (F-2), add an amino acid converting reagent at the appropriate time for proline detection, and monitor leak conditions. Simultaneously, fluorescence data from the fluorimeter detector will be collected and stored in memory. Peak detection, peak separation, and calculation of component concentrations will then be done either during or after completion of the run, depending upon the complexity of the system under analysis. Since the Intel 4004 based solvent switching system is working satisfactorily, initial work on the new microcomputer system has focused on providing automated acquisition and processing of data from the amino acid analyzer.

The microcomputer system is based on a DEC LSI-11 microcomputer. The basic computer module includes a 16-bit central processing unit with fixed and floating-point capability and 4K of 16-bit RAM memory. Two DEC 16-bit dual input/output modules permit interfacing with an inexpensive integrated circuit 12-bit analog-to-digital converter, an 18-column alphanumeric printer, and an alphanumeric keyboard with 18 special function keys. An inexpensive integrated circuit instrumentation amplifier, followed by an operational amplifier based filter, provide processing of the analog output from the amino acid analyzer prior to analog-to-digital conversion. Two DEC serial interface modules permit program modification and debugging from a Teletype or CRT terminal and communication with other off-line processors. Several PDP-11 systems

are available for program development, using the serial interface module to load the assembled binary program into the LSI-11. A 4K-word core memory module provides capability for long term program storage, yet is readily alterable, thus convenient during initial checkout of the microcomputer system. We presently are involved in verifying the hardware and developing the software required in this initial system design.

In setting up this first laboratory microcomputer system, the requirements of all the potential applications mentioned above were considered so as to insure that the microcomputer system design would be readily adaptable to new uses. Enough capacity has been included in the initial microcomputer system so that further applications will not require a redesign of system components.

Use of the simple scheme of parallel data transmission between each system component insures that the system components will be essentially independent of the microprocessor. That is, although an LSI-11 processor is used initially, the system hardware is designed to be compatible with several microprocessors. As other more suitable microprocessors become available, or for those applications where all the capabilities of an LSI-11 processor are not required, suitable or economically feasible, another processor may be selected without redesign of the entire system.

Initially, program development was done using the LSI-11 paper-tape software package loaded from a Teletype. In the past year an LSI-11 dual flexible disk system was made available to us on a temporary basis. Hence, to simplify and speed up program and system development, we acquired a DEC VT-55 CRT terminal, the RT-11 operating system, and RT-11 FORTRAN. These are presently being used for all software development.

The dual flexible disks and all of the system hardware are housed in a mobile cart which can be easily moved to the site of the amino acid analyzer or other laboratory instrumentation. Thus, program and system development and debugging can be done on site. Once an application is completed, hardware required for that application will be housed in a box with a control and monitoring panel in front and connectors in the rear for the analog and digital I/O, the alphanumeric printer, and the keyboard. This dedicated system will be left at the instrument site. The mobile flexible-disk-based development system, however, will permit quick and easy maintenance or system improvement should problems subsequently develop, or should modifications and improvements to the system be necessary.

(1) J. R. Benson and P. E. Hare, "o-Phthaladehyde: Fluorogenic Detection of Primary Amines in the Picomole Range. Comparison with Fluoroescamine and Ninhydrin," Proceedings of the National Academy of Sciences, vol. 72, no. 2, pp. 619-622, 1975.

F-2. A High-Sensitivity Microprocessor-Controlled Amino-Acid Analyzer

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Support: RR 00396
CA 08759
GM 13925

The MCS-4 microprocessor controlled amino-acid analyzer (PR-12, F-2) has passed through an extended testing period and is now in routine operation. This new analyzer uses high-pressure liquid chromatography and a sensitive fluorescent reagent to achieve faster analyses with much greater sensitivity than standard analyzers. The MCS-4 microprocessor system controls a multiple-port valve, selecting the sequence and duration of buffer solutions pumped through the column during the separation. The novelty of the method, its sensitivity, and speed, required extensive experimentation to determine the correct timing sequence for each buffer to insure clean separations of the amino acids and elimination of competing artifact peaks. The resulting system can yield quantitative analyses on hydrolysates from much smaller peptide samples, extending the range of proteins that can be analyzed. The analyzer has been used to compare total acid hydrolyzates of polypeptides isolated from the yolk lipoprotein system.[1] This is part of a long range study to determine the structure of this macromolecular system. The instrument is currently being used to determine amino acids and sugar amines from glycoprotein samples.

[1] D. H. Ohlendorf, G. R. Barbarash, A. Trout, C. Kent, L. J. Banaszak, "Lipid and Polypeptide Components of Crystalline Lipoprotein," Journal of Biological Chemistry, in press.

F-3. Cary Spectrophotometer Paper-Tape-Punch Interface

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Support: RR 00396
HL 12820
HL 14147

The Cary spectrophotometer paper-tape-punch interface, whose design was described in a previous report (PR-12, F-3), has been constructed and tested. This interface permits automatic data acquisition from a Cary 118C Double Beam Spectrophotometer.

The interface operates through the digital panel meter of the spectrophotometer to capture binary-coded-decimal (BCD) data normally displayed by the panel meter. After converting these BCD data to eight-bit ASCII code, the paper-tape-punch interface transmits the ASCII code serially at 110 baud to a Teletype equipped with a paper-tape punch. Each set of data is transmitted with the current reading of a three-digit counter driven by an 11 cps clock. This counter indicates the relative time or wavelength since data acquisition began.

After a single character header consisting of one decimal point character, the punched paper-tape generated by the interface consists of sets of eight characters, each set of eight characters being followed by a carriage return and line feed. The inclusion of carriage-return and line-feed characters following each reading slows the rate at which data can be acquired to one sample per second from the one sample per 0.8 second rate reported previously. However, the inclusion of these characters permits generation of a hard copy listing of the data being collected while the paper-tape is being punched. Persons using the interface can then examine the data before attempting to process the tape. Inclusion of these characters also permits input and processing of the paper-tape by either a programmable calculator or a minicomputer equipped with a paper-tape reader. The final paper-tape-punch interface design has been completely documented and a user's manual has been prepared.

Using this system, calcium binding to prothrombin Fragment 1 was measured on a Cary spectrophotometer. Output tapes were read onto PDP-12 minicomputer disk files, in a form which permitted preliminary numerical analysis. These binding-rate studies form part of a study employing mathematical modeling of the enzyme kinetics of blood coagulation.

F-4. Parameter Estimation for Mass-Spectrometry Data

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Support: RR 00396
RR 00954

In many gas chromatograph/mass spectrometry (GC/MS) studies, the compound of interest is present in extremely small amounts. Because of noise in the GC/MS process, it is difficult to measure these small amounts with current techniques. We are investigating various statistical and signal processing techniques to determine if they provide improved characterization over methods currently used in this laboratory for analyzing GC/MS data.

For our first effort we designed a least-squares estimation procedure to be applied to studies in which a known amount of a reference compound is added to the sample solution in a concentration which is large compared to the unknown compound. After partial purification, derivatization, and injection in the GC inlet, the mass spectrometer records the ion intensity at two masses as a function of time. The first mass corresponds to a fragment ion from the reference compound, while the second mass represents the corresponding fragment ion from the sample compound. The least-squares method is used to compute the ratio of the "amplitudes" of the two GC peaks formed by the ion signals at the two masses. The baseline is first subtracted from the reference peak, which is then translated in time so that the maxima of the reference peak and the sample peak coincide. The reference peak is then scaled to effect a least-squares fit to the sample peak. The scale factor that produces the fit is the desired ratio of the amplitudes. The accuracy of this method was measured by computing the ratio of morphine to deuterated morphine, using mass-spectrometer data from a mixture of known composition. For comparison, our current method for directly computing the ratio of peak heights or peak areas was applied to the same data. It was found that the fitting procedure was only slightly more accurate.

The next step in this investigation will be to characterize the types of noise typically found in mass-spectrometer data. This information will enable us to apply the appropriate statistical inference and estimation techniques to the GC/MS data.

G. Speech and Hearing

In collaboration with Central Institute for the Deaf (CID), digital instruments and systems that are specifically tailored to be effective in furthering speech-and-hearing research have been developed. The work began with the implementation of a computer system for processing sampled speech and the concurrent development of a Random-Access, Programmable (RAP-I) digital recorder which stores and plays back complex sounds useful in psychoacoustic experiments. The Speech-and-Hearing Computer System and RAP-I are storage compatible so that sounds synthesized or recorded on one device can be played back or analyzed on the other. RAP-III, a more flexible minicomputer-based version of RAP-I, is now in development for use in various laboratories at CID for generating stimuli, controlling experimental protocol, and for collecting data. A central computer system has been installed and will provide sophisticated programming tools and data processing support for these satellite systems.

These digital systems have made it possible to address a number of problems in speech-and-hearing research. Resonator models have been programmed and calibrated so that speech-like sounds can be synthesized; an adaptive speech-discrimination test (MEGS) has been developed; methods of speech analysis, including linear prediction as it applies to acoustic models of the vocal tract, have been studied; a means to measure glottal waveforms of normal and deaf people has been developed to evaluate the physical basis of linguistically significant changes in pitch; digital techniques have been applied to the synthesis of calibrated complex tones for studying cochlear microphonics; and we have begun the study of alternate sensory modalities for nonauditory speech reception.

A major effort continues to focus on mathematically modeling the hydromechanical behavior of the inner ear. A previously developed three-dimensional model was unsuitable for time-domain implementation. Therefore, we have developed a two-dimensional model that is capable of simulating, in time, the mechanical response of the cochlea to arbitrary stimuli. The mathematical development, drawing on experiences with the earlier model, resulted in a closed-form expression describing the motion of the perilymph and basilar membrane at their adjoining boundary. An important feature of the current model is its physical basis, with the structure of the cochlea represented by two fluid-filled rectangular chambers separated by a partition defined by its specific acoustic impedance. The partition impedance and other physical characteristics are easily identified and defined as parameters of the mathematical expression. Implementation of the model in a digital form is motivated by the desire to have close control of the independent variables, time (run, stop, slow motion), convenient access to model parameters, and responses generated in digital form, thus simplifying the addition of neural models or pattern-processing schemes. One of our principle interests is to study the response of the model to a variety of speech sounds.

G-1. A Two Dimensional Model of Cochlear Mechanics

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Support: RR 00396

The difficulty associated with performing experiments on the cochlea suggests that modeling its hydromechanical behavior will aid in developing an understanding of cochlear mechanics. We have completed the derivation and implementation of a two-dimensional model[1] that is capable of simulating the temporal mechanical-response of the cochlea to arbitrary stimuli. The mathematical derivation resulted in a closed form expression describing the motion of the perilymph and basilar membrane along their adjoining boundary. The model we are using has the important feature of being physically based, resulting in model parameters that are related to the physical properties of the cochlea. For example, the partition boundary is expressed in terms of its specific acoustic impedance with k_i (the stiffness), r_i (the damping), and m_i (the mass), each defined at point i along the partition. The expression

$$\ddot{x}_i = \sum_{j=1}^{N} G_{ij}(M_j \ddot{x}_j + R_j \dot{x}_j + K_j x_j) + H_i P_s$$

relates the partition motion parameters (x_i, $\dot{x}_i$, $\ddot{x}_i$), the fluid system characteristics (G_{ij}, H_i), the partition impedance (M_i, R_i, K_i), and the pressure at the stapes (P_s).

During the past year we have implemented the model algorithm on the MMS-X system[2] resulting in an order of magnitude improvement in performance over previous versions. The restructured macromodule matrix multiplier embodied in the MMS-X system is used to perform the required numerical calculations. The graphic facilities of the MMS-X greatly enhance the presentation of results. The structure of the current implementation is given in Figure 1.

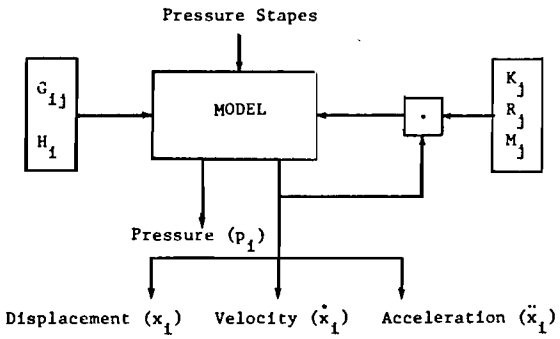

FIGURE 1

Performance of the simulation is not limited by the time required for calculation of fluid or partition parameters since G and H are constant for a given set of morphometrics and K_j, R_j, and M_j are constant except in the case where the partition parameters are varied by the partition pressure or motion. The only independent variable at run time is the stapes pressure. The motion of the partition and the pressure across it are calculated as a response to the applied stapes pressure.

In the coming year we will begin studies, using the present implementation, to discover the effect of parameter variation on the model response and to investigate the partition response to speech waveform stimuli (G-2). Because of the desire to use the model in an interactive environment we anticipate the need to improve performance beyond the current level. A restructured macromodular system tailored to fit the algorithm and appended to the MMS-X system is expected to yield the required performance improvements.

(1) B. F. Spenner, "A Two Dimensional Model of Cochlear Mechanics," D.Sc. Dissertation, Washington University, St. Louis, Missouri, August 1976.

(2) F. U. Rosenberger, "MMS-X Control and Parameter Blocks," Washington University Computer Systems Laboratory, Technical Memorandum No. 227, September 1976.

G-2. Analysis of Speech Sounds Using a Cochlear Model

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Support: RR 00396
NS 03856

The method by which humans process speech information is still essentially a mystery even after years of study that have seen the application of many analysis techniques. Spectral analysis of speech waveforms and vocal tract modeling are two examples of techniques that have been applied in speech research. In spite of notable advances in the knowledge of speech it has not yet proven possible to establish simple, invariant relations between the acoustic description of speech sounds and their phonetic features or categories. We argue that this is due, in part, to a failure of current speech analyzers to adequately model the analysis performed by the mammalian auditory system. It seems appropriate, therefore, to apply the cochlear model (G-1) to the problem

of analyzing speech and to process speech in a manner that parallels as closely as possible the operations performed by the auditory system.

Our approach is to analyze sounds after they have been processed by three sequential analyzers. The first of these is a biophysical model of the outer, middle, and inner ears. The second analyzer is designed to simulate as closely as possible the mechanical-neural transduction performed by the mammalian auditory system. The third analyzer utilizes algorithms designed to extract the significant factors from the spatially-distributed output of the first two analyzers.

Preliminary work started during the last year has provided an initial look at the output of the first two analyzers. The effect of the outer and middle ears was introduced into the first analyzer by passing the recorded free-field signal through a filter with a transfer function that approximated the operating characteristics of these two components of the auditory system. This preprocessed signal then was used as the stimulus for the cochlear model. The second analyzer was implemented as a simple peak detector for this preliminary study. The responses that were recorded at the output of the second analyzer for three different speech sounds are presented in Figure 1.

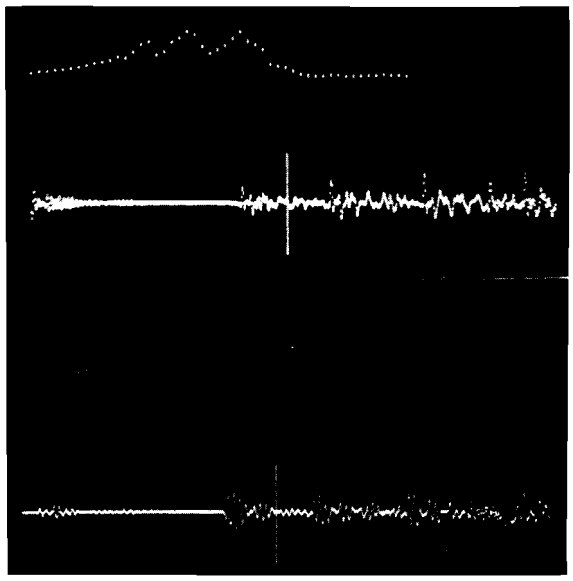

Figure 1. The top trace on each plate illustrates the second analyzer response to the particular stimulus plotted as a function of distance along the partition with the basal response to the left. The portion of the stimulus waveform included in the response extends from the beginning of the trace to the vertical line.

G-3. Computer Systems for Auditory Research

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An outgrowth of the BCL-CID collaborative project is a plan for economical deployment of small computer systems in the research laboratories of CID. This plan includes a central computer system and compatible, but simpler, satellite systems, with one such satellite system serving an individual laboratory. Much of our effort this year has involved the selection, purchase, and installation of the central system and the completion of the design, assembly, and checkout of a prototype satellite system.

The central system consists of a Data General Eclipse S/200 computer with 32k words of memory, a 10 megabyte system disk, and a floating point processor. Bench mark tests indicate that this system will be an order of magnitude faster than the Speech-and-Hearing System that we have been using, thereby significantly increasing our capability for synthesizing and analyzing speech sounds and for simulating physiological models of hearing. The central system includes a Tektronix 4006-1 graphics terminal for program entry and graphic display and a Varian 4211 electrostatic printer/plotter for generating hard copy of graphical results. The printer/plotter also serves as a 500-line-per-minute printer for listing programs and tabulated results. All system software, including a real-time disk operating system, FORTRAN IV and FORTRAN V, ALGOL and BASIC, have been tested and verified. Software for the electrostatic printer/plotter has been modified for our system configuration. A number of utility programs has been developed to use with the satellite system interfaced to the Eclipse.

The design of the satellite system (RAP-III) has been completed and a prototype version is now operational. RAP-III is an extended version of the RAP system that was developed at BCL about four years ago and has been used extensively since that time in psychoacoustic experiments at CID. RAP-III consists of the following subsystems: 1) a Pertec 3000 series dual disk drive and controller for mass storage of programs and sampled data, 2) a two-channel analog subsystem for the sampling and reconstruction of analog signals, 3) a two-channel laboratory interface consisting of input and output control lines, event timers, and a programmable clock, 4) a serial interface and keyboard display terminal, 5) a 16 bit × 16k word semiconductor memory for program execution and data buffering, and 6) a Data General Nova 1200 CPU board. Since the Nova and Eclipse I/O bus structures are identical it is possible

to connect a RAP-III system, without the memory and CPU subsystems, directly to the Eclipse bus with an extender cable. One RAP-III system will be installed as part of the Eclipse system to facilitate developing application programs for free-standing RAP systems. Programs and sampled data can be exchanged between systems on the removable disk cartridges.

Special features of the RAP-III subsystems include: 1) the data format of the disk controller can be altered by program instructions to accommodate the Eclipse operating system file structure in addition to the RAP-I and the Speech-and-Hearing System disk formats, thereby facilitating data interchange among these three systems, 2) the analog subsystem utilizes direct memory block transfers to simplify programming and to reduce timing constraints that often arise in complex programs, 3) both the disk controller and analog subsystem can be set to use only reserved memory locations to protect the program memory area, and 4) the laboratory interface contains a variety of functions that can replace special laboratory equipment for control and data collection during experimentation.

Application programs for the RAP system are presently under development, including a program to control and collect data in experiments of the Comparative Psychoacoustics Laboratory. The first system will be installed in this laboratory this summer after programming is completed. A second RAP-III system is also under construction at this time and future plans include the construction of additional RAP-III systems for the clinic and other research laboratories at CID.

G-4. Voice Source Characteristics

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Support: RR 00396
NS 03856

Glottal volume velocity waveforms from male and female adults have been collected by means of a reflectionless vocal tract terminator. This method employs a long metal tube to act as a pseudo-infinite termination. When a subject phonates a neutral vowel into the tube a microphone within the tube picks up the glottal volume velocity waveform since the termination of the tube provided by a foam wedge nearly eliminates the resonances of the vocal tract. The principal advantages of this method are that it is physically uncomplicated and does not involve any discomfort or extensive preparation on the part of the human subject, it is highly noise resistant, and allows analysis of the glottal waveform in real time. In addition, it appears to provide data on the velocity

waveform as accurately as other methods.

The steel tube is 1.8 meters long with an inside diameter of 2.2 cm and is divided into two equally long parts joined on the outside by a metal sleeve. The tube is constructed in two parts to facilitate cleaning and handling. The mouthpiece of hard nylon has the same inner diameter as the inside of the tube and is detachable for easy cleaning. A Thermoelectron (model 5333-C) microphone fits into the tube in such a way that its surface (12.7 mm diameter) is flush with the inner wall of the tube. Polyurethane foam, used to construct the wedge, is cut into an approximately 90 cm long wedge shape, the base end of which is slightly larger than the inside diameter of the tube.

Subjects provided samples of the following types of phonation:

1. Normal voice, soft voice, loud voice,

2. Falsetto voice and creaky voice ("vocal fry"),

3. Rising and falling F_0 glides, such as are typical of words with interrogative and declarative intonation in English,

4. Stressed and unstressed syllables: three-syllable "words" with primary lexical stress on one of the three syllables, i.e., /UH-uh-uh/, /uh-UH-uh/, /uh-uh-UH/.

During the recording of subjects the signal from the microphone is amplified and digitized into 12 bit samples at a 20 kHz sampling rate. The glottal waves are recorded on disk on the Speech-and-Hearing System. The analysis program displays the glottal waveform on a scope and allows the examiner to isolate individual glottal periods by the use of cursors which pick out zero-crossings of the waveform. For each period selected in this way the program calculates rms intensity, fundamental frequency, and both the amplitude and phase spectra.

Analysis of the collected data indicates a wide variation of the glottal waveform shape, its rms intensity, fundamental frequency, phase spectrum and amplitude spectrum. It is observed that as the fundamental frequency changes over time during the production of running speech the glottal source varies in two different ways that are associated with different linguistic conditions. In monosyllables with interrogative intonation the harmonic relations become steeper as the fundamental frequency rises. In words with declarative or falling intonation the harmonic relations tend to remain the same despite a decrease of the fundamental frequency. Harmonic relations in the spectrum also remain the same when periods of different fundamental frequency are compared from stressed and unstressed syllables.

The different types of change in the glottal wave appear to correspond to different types of physiological control over the change of fundamental frequency. This is being investigated by means of the Ishizaka-Flanagan

two-mass model of vocal fold vibration. The vocal folds are modeled as a self-oscillating source with two masses representing each vocal fold and the tract is modeled as a transmission line, terminating with an impedance equivalent to the radiation impedance of air at the lips. The masses representing each vocal fold are parts of mechanical oscillators with compliance and damping. The model is implemented by using the Speech-and-Hearing System and allows the user to specify (1) the relative size of the vocal folds (corresponding to those of the male, female, or child), (2) the vocal tract shape (area), (3) the amount of vocal fold tension, and (4) the amount of sub-glottal air pressure. Both sub-glottal air pressure and vocal fold tension can be varied over time. For a given set of specified parameters the model synthesizes the glottal volume velocity wave, the glottal area wave, and the corresponding speech wave. From a comparison of these synthesized waveforms with the natural glottal waveforms we can tentatively conclude that (1) sub-glottal air pressure is primarily responsible for the change in fundamental frequency found in declarative (falling F_0) syllables, while increased vocal fold tension appears responsible for the rise in fundamental frequency over the course of interrogative (rising F_0) syllables, (2) the higher fundamental frequency of stressed syllables appears due to increased vocal fold tension, while the change of F_0 over the course of either a stressed or unstressed syllable appears due to a rise or fall in the sub-glottal air pressure.

Further investigation will include the collection of voice source data from speakers with hearing impairment and from speakers of languages other than English.

G-5. Experiments in Tactile Loudness with a Single Channel Electrocutaneous Stimulator

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Support: RR 00396
NS 03856

At present there is no generally useful alternative to the high-power hearing aid as a sensory aid for the profoundly deaf. While improvements in speech-reception capabilities have been demonstrated through the use of experimental devices, these improvements are usually modest and seem to be related to the low-channel capacities of the displays. Practical applications of the demonstrated improvements have been limited by a host of problems related to actual use, such as power consumption,

convenience, stability of the display under everyday conditions, and so forth.

Recently F. A. Saunders, at the Smith Kettlewell Institute in San Francisco, has developed a method of electrocutaneous stimulation that may be superior to mechanical vibrators in applications involving wearable devices. The electrocutaneous method provides a distinct tactile sensation and may result in greatly reduced electrical power requirements. The electrodes can be inexpensively fabricated in a variety of configurations. Because of the possible advantages of this method we have undertaken a psychophysical study of the sensations produced by a single stimulator of the Saunders type. The electrode driver amplifier has been interfaced to the Speech-and-Hearing System which is programmed to deliver a burst of N biphasic constant current pulses at a rate burst of R bursts per second.

In our present study the loudness of the electrocutaneous stimulus is evaluated by matching it with the loudness of a 500 Hz pure tone. The burst rate (R) is fixed at 30 Hz. The duration of each pulse (τ) and the number of pulses per burst (N) are varied. The electrode is placed on the abdomen, about four inches to the right of the midline and one inch above the level of the navel. Values of τ were selected to be either 4.5, 6.0, or 9.0 μsec while N was varied from 1 to 150 pulses per burst.

Often we are able to obtain a dynamic range of matched loudness levels of 60 dB. If the data are shifted to eliminate the large day-to-day variability the matching ratio between the rms current in the burst-period (in dB) and the loudness level of the tone is 4. Empirically this means that a factor of 3 increase in N produces a 20 dB change in the level of the matched tone. Unfortunately, at some locations and on some days the loudness level of the electrocutaneous sensation will not grow to the matched value in excess of 30 or 40 phons.

The variability of the electrocutaneous sensation is a major problem. Within a run the range of tone values matched for any one value of N is about $\pm$ 10 dB, which is quite large. Unfortunately, between loci or days, variability in the tone values matched to a given N may be as great as $\pm$ 20 dB. Many hours have been spent trying to eliminate possible sources of variability. The skin is prepared by wiping with alcohol, by using cellophane tape to remove the surface layer of dead cells, and by moistening the area with physiological saline. Warm-up effects are reduced by having a period of stimulation prior to the collection of data and, finally, habituation is eliminated by using 0.5-sec periods of stimulation spaced at 4.5-sec intervals.

It may be that the most important remaining source of variability is the physiological state of the observer, especially the blood flow and the condition of the tissue between the nerve endings and the electrode. Since we have little control over these variables, perhaps the design of electrocutaneous displays will have to allow for the observed variability from site to site and from day to day.

G-6. Observations on the "Sharpness" and "Modulation" of Electrocutaneous Stimulation at a Burst Rate of 30 Hz

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K. W. Grant, Central Institute for the Deaf
J. D. Miller, Ph.D., Central Institute for the Deaf

Support: RR 00396
NS 03856

While conducting our observations on the loudness of electrocutaneous stimulus (G-5) we noticed that sensation seemed to vary in "area" that is along a dull-sharp dimension and in degree of modulation that is along a smooth-flutter dimension (this was true even though R is held constant at 30 Hz). We hoped that the three nearly independent qualities of loudness, area, and modulation could be related to combinations of N, the number of pulses per burst, and τ, the pulse duration. This possibility was examined in two ways. The first approach was to fix N and have the subject vary τ and locate category boundaries, that is, the changes from dull to sharp and smooth to flutter. The other approach was to conduct the usual loudness matching experiment, but also require the subject to rate the tactile quality for area and modulation on 5-point scales. The first approach was encouraging as quality boundaries could be observed and contour lines drawn in the N-τ space for a given day. Unfortunately, day-to-day variability is so great that study of these possible dimensions is too difficult to pursue and their use in an electrocutaneous display would probably be fruitless until a better understanding and control of the day-to-day variability can be achieved.

G-7. Psychoacoustic Studies Involving Digitally Processed Natural and Synthetic Speech Sounds

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Support: RR 00396
NS 03856

Since the inception of the BCL-CID collaborative effort there have been many studies of a psychoacoustic nature that have utilized the digital

capabilities resulting from the joint effort. These have included the tailoring and randomization of speech materials for the evaluation of hearing aid designs,[1,2] the development of a novel adaptive procedure for the testing of speech-reception capabilities,[3] the psychoacoustic study of the boundaries between speech-sound categories,[4,5] and the study of the perception of speech-sound categories by human infants[6-10] and animals.[11-15] Some of these continuing projects are described in more detail below.

The boundary between aspirated plosive consonants /ptk/ and similar unaspirated ones /bdg/ has been studied extensively using synthetic speech. This is done by exciting appropriate resonators, first with noise (aspiration), then with a glottal wave (buzz or voice). The time between the onset of the noise and the later onset of buzz or voice is called the voice-onset time or VOT. Past research has indicated that small changes in VOT are discriminated most easily near the aspirated/unaspirated perceptual boundaries. Our own results[4] confirm this now traditional finding when the listeners are relatively untrained but native speakers of English and when a large number of possible VOTs are included in each test run. If only one VOT is studied at a time and the listeners are so trained, results similar to the traditional Weber's Law are obtained. This suggests that the usual locus of best discrimination near the aspirated/unaspirated boundary is dependent, in part, upon the demands on the subject's attention and memory which are present when a variety of stimuli are intermixed within a run.

We have explored factors involved in vowel boundaries[5] also and, more recently, the role of glottal wave in the perception of unified auditory percepts.

One of our continuing uses of synthetic speech has been the study of speech perception during infancy. Earlier we had shown that differences in vowel color, for example, the difference between "ah" and "ee", is quite noticeable to infants of four-to-sixteen weeks of age, while changes in the pitch contour of these vowels are less salient.[6,7] More recently we have synthesized a set of vowels and dipthongs which simulate those produced by children, women, and men. These were synthesized with rising or rise-fall pitch contours. Studies done by Kuhl at the University of Washington in Seattle confirm and extend previous results. It is found that infants of about 6 months of age, when trained with male tokens of "ah" vs. "ee" or "ah" vs. "aw", quickly transfer such training to the tokens that simulate the female and the child. Similar results are not observed for differences in pitch contours.[8,9]

These results strongly suggest that the members' vowel categories are inherently similar so that vowel categories can be learned readily. It appears that the acoustic correlates of the phonetic message are attention-arresting in comparison with correlates of talkers' age, sex, or intonation.

Another use of synthetic speech has been in the comparative psychoacoustics of speech perception. Earlier experiments indicated that the chinchilla, a rodent, could distinguish the sound categories "ee" and "ah" in spite of random irrelevant variations in sound level, talker, pitch level, and pitch contour. It was shown also that chinchillas can similarly discriminate "t" from "d" when these initiate a syllable, independent of the vowel or the talker.[12] Using synthetic speech, we have been able to show that these discriminations by chinchillas and men are based on similar acoustic cues.[13]

Presently, through synthesis, the role of the pattern of energy distribution along the length of the basilar membrane is being explored as an explanation of species differences and transposition. For example, a synthetic series, "bae-dae-gae", seems to be heard as only two categories by the chinchilla.[15] When we synthesize sounds that we believe produce similar patterns on the human basilar membrane the human seems to hear only two categories, bae and dae, in a manner which may be similar to that of the chinchilla. We have also transposed these stimuli along the human basilar membrane so that the distances between concentrations of energy in millimeters are maintained. In this case, while the sounds change drastically in the overall "pitch of their timbre", the phonetic identities are nearly maintained.

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G-8. Analysis of Cochlear Nonlinearities Through Study of Microphonic "Signatures"

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Support: RR 00396
NS 03856

Cochlear microphonic voltage (CM), as recorded using gross differential electrodes, provides an important indicator for the auditory processing along the basilar membrane that precedes the transduction to neural responses. The principle objective of this project has been the measurement of frequency-dependent nonlinearities in the cochlear microphonic responses of the chinchilla. In particular, experiments have been directed towards examining distortion products that are known to be present in the responses of individual auditory nerve fibers and are perceptible to human listeners.

To study these distortion products three pairs of differential electrodes are used to measure responses from the basal (CM_1), second (CM_2), and third (CM_3) cochlear turns. The stimulus waveforms are synthesized digitially by inverse Fast Fourier Transforms and include corrections to compensate exactly for the frequency characteristics of the recording system, the transducer, the acoustic coupling into the animal's ear with the acoustic resonances peculiar to the ear canal, the acoustic load presented to the transducer by the ear, and tympanic membrane of individual chinchillas. The waveforms are synthesized on the Speech-and-Hearing System and then stored on a removable disk cartridge. The actual data collection in the laboratory is controlled by a classic LINC which is interfaced to a dual disk unit (mRAP) that uses the same removable disk cartridges. In addition, mRAP has an 8k-word memory accessible to the LINC and its own A/D and D/A converters. Responses are recorded contemporaneously with signal presentation by interleaving the A/D function with the D/A function through the 4096 words from a track. Signal-to-noise ratio is enhanced by averaging over a large number of points. As a result double-precision addition is required to perform the response averaging. Response waveforms normalized to 12 bits are obtained by the LINC and stored on the removable disk cartridge of mRAP for subsequent analysis into components of its Fourier Transform on the Speech-and-Hearing System. Using these signal processing procedures, a 60-dB signal-to-noise ratio is attained for the precisely controlled arbitrary sounds.

The signals most commonly used have been single tones, complexes of two tones with equal sound pressures and fixed phases, or 58-component waveforms with phase selected to produce bandlimited impulses or psuedo-random noise. In each cochlear turn the amplitudes of the frequency response function for single tones reflects appropriately the low-pass tuning of the Békésy traveling wave and the phases reflect the traveling

wave delays. For a normal cochlea nonlinearities appear in several ways. The growth of response with level is nonlinear, even at low levels, for frequencies near or slightly above those for which each turn shows greatest sensitivity. The failure of linear superposition, or two-tone interference, is a prominent characteristic of the nonlinear responses to pairs of tones. Also, frequency components characteristic of harmonic and intermodulation distortion are relatively abundant, but the phases of these components are not related to the phases of the primaries in a consistent manner. At low levels the frequency responses to the wideband signal with all components in cosine phase are similar to those for single tones, but become even more nonlinear with increasing level. At moderate levels the wideband signal with its different set of phases elicits a complicated nonlinear response so characteristic of the level, phase, and waveform that we have called these wideband responses CM "signatures".

As signal level is increased the simple low-pass character of the frequency response to pure tones begins to show irregular lobes in the range of frequencies that were successfully rejected at lower levels. These lobes suggest that the responses arise from multiple sources with amplitudes and phases that change differently with frequency and level. For example, as sensitivity of CM_2 falls with frequency the recorded voltages arising locally may fall below the level of the CM_1 voltages, spreading apically from the basal turn. It has long been recognized that cochlear microphonic potentials recorded at a given site do not represent cochlear events at that position in a simple way. One of the complicating factors is that the recorded potentials are produced by a spatially-distributed array of generators located along electrically-conductive channels. Although the differential records clearly favor potentials arising between the electrodes, the attenuation with distance and the common mode rejection for potentials arising at a distance do not completely eliminate these from the records. During the past year we tried to assess some of the consequences of this anatomical arrangement for linear and nonlinear aspects of the gross CM.

In the chinchilla the Békésy traveling wave confines the action of a 3 kHz high-pass band of noise to the basal turn with only minimal disturbance in the second turn. With exposures to this noise at 100 dB SPL, CM_1 may be reduced significantly by fatigue (-25 dB) in about 2 hours and maintained in this state for long periods by multiplexing test signals with continuing noise exposure. In this fatigued state the response characteristics of CM_2 are simplified greatly even though overall sensitivity and maximum voltages are changed little. The irregular lobes, the manifest nonlinearity at low levels, and two-tone interference are absent or much reduced. Furthermore, the phases of distortion products now relate consistently to the phases of the primary response components. The remaining nonlinearities are amplitude-dependent, but may no longer be frequency-dependent. The elimination at the source of remote contributions to CM_2 represents a significant addition to our understanding of cochlear nonlinearity. However, after this "treatment" with noise, there are other changes in the frequency responses shown by CM_2, that we have not yet been able to explain.

G-9. A System for Linear Predictor/Spectral Analysis of Speech Signals

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The Linear Prediction (LP) analysis system developed as a tool to determine the vocal tract area function has been thoroughly revised and modified. The LP algorithm is preserved, but the rest of the system for recording the speech signals, saving the data on the disk, selecting the data for the preprocessor, the preprocessor displays and options, and the display of the results has been completely changed. (The system has also been expanded to include spectral analysis in addition to the LP analysis.) At present the system uses the Tektronix scope display unit and the keyboard for interactive examination and analysis of the speech signals. The system is currently being used in a study of the glottal wave (G-4).

The LP/Spectral analysis system has the following capabilities. Speech data can be read from specified RAP tracks or recorded through the microphone. These data can be displayed on 75 ms frames and a 25.5 ms of data can be selected by using a variable pointer controlled by the knobs on the keyboard. The selected data can be displayed separately while the initial and the final pointers of a variable "window" can be controlled by knobs on the keyboard or can be set to the zero crossings of the signal. The signal can be displayed on an expanded time scale in order to study its detailed structure or it can be preprocessed by specifying the poles and zeros of a digital filter. The data can be further quantized to a specified number of bits or further windowed with a Hamming window. Samples within the window can be neglected to effectively cut down the sampling rate or a specified amount of random noise can be added to the signal. The user can perform LP or spectral analysis. The results include a display of the vocal tract area function, a comparison of the LP areas with standard ones, an optimization of the LP areas so that the right number of areas with the right multiplication factor for the areas are computed, and a display of the LP and the standard areas together. Also, the LP transfer function can be displayed, the poles of the LP filter and the vowel formants can be computed and displayed, and the power and phase spectra of the signal can be shown both on linear and logarithmic frequency scale. For convenience an option to display the power spectrum of the windowed signal is included. The system can be used to record and examine analog signals and store these signals on RAP disk cartridges.

G-10. Determination of the Vocal Tract Area Function and the Glottal Flow During Phonation from Input/Output Measurements

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Information regarding the shape of the vocal tract, its transmission characteristics, and also the shape of the glottal wave during phonation is of interest in speech studies and may have practical applications in the development of training-aids for the deaf. Our work with Linear Prediction (LP) analysis indicates that improved performance may be obtained if an estimate of the glottal source function can be obtained.(1)

We have proposed a model for the vibration of the throat wall, in which the larynx with its various cartilages, muscles, and tissues is represented as a lumped-parameter mechanical system for which there are two inputs and one output. The inputs are the supraglottal sound pressure and the net dynamic mechanical force exerted by the vibrating vocal folds on the thyroid cartilage and the output is the vibrational velocity of the throat wall. The approach that is being taken is the following. The transfer function of the throat wall, relating throat wall vibration to the supraglottal pressure, will be measured, along with the contribution of the mechanical forces to the wall vibration. From a measurement of the accelerometer signal placed on the throat during phonation we can then subtract the component due to the mechanical forces and inverse filter the resulting signal to obtain the supraglottal sound pressure. From this signal and the measured speech signal we can study the tract area function and the glottal flow problems.

We are presently conducting the following experiments. The purpose of the first is to determine the transfer function of the throat wall considering the supraglottal sound pressure as the input and the wall vibration as the output. Since it is difficult to control and monitor the supraglottal pressure directly we are employing the reciprocity principle and are measuring the velocity of the inside surface of the wall for an external vibratory force signal. The inside velocity can be measured by using the glottal tube (G-4) with the subject holding a near neutral tract shape and a closed glottis. It has been shown that under these conditions considerable departures from the neutral shape should produce only a minor filtering of the velocity signal as measured by the microphone in the glottal tube.

The purpose of the second experiment is to study the contributions of the mechanical forces to the wall vibration. Here the subject phonates a neutral vowel into the glottal tube and simultaneous measurements of the glottal tube signal and the accelerometer signal are made. To

a first approximation the glottal tube signal can be taken as the supraglottal pressure signal. Now the contribution of the supraglottal sound pressure to the wall vibration can be computed easily since we know the pressure and the measured transfer function of the wall from the vibrator experiment described above. Under the assumption that the laryngeal mechanical system is linear to the two inputs the contribution of the mechanical forces to the wall vibration can be determined from the measured vibratory signal and the predicted one due to the acoustic pressure alone.

In the last experiment the subject phonates a sustained vowel and recordings of the speech and the accelerometer signals are made simultaneously. The procedure is to determine the supraglottal sound pressure corresponding to that particular vowel from the measured wall vibration, given the contribution of the mechanical forces and the transfer function characteristic of the wall. The volume velocity of air at the lips can be found by integrating the speech signal where it is assumed that the lip radiation function can be approximated by a simple differentiator. We have developed algorithms which determine the vocal tract area function and the glottal wave by using the supraglottal sound pressure and the lip volume velocity signals.

We are currently using a B&K Type 4810 Mini-shaker as the vibrator and a B&K Type 8000 impedance head to monitor the force and the acceleration signals in the vibrator experiment. Preliminary results suggest that the transfer function of the throat wall has a characteristic that falls off at a rate -12 to -15 dB octave in the range 100 Hz to 2 kHz. The input impedance at the wall increases at approximately +6 dB/octave. We have developed a mechanical model for the wall, consisting of 5 parameters (2 masses, 2 springs, and a damper), for which the experimental data agree with the model behavior below 2 kHz. We have performed the glottal tube and the speech experiments also and noticed that the speech formants can be observed in the accelerometer signal. We plan to do more detailed studies of the wall transfer function and the contribution of the mechanical forces to the wall vibration in the near future.

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H. Central Nervous System Diseases and Electroencephalogram Analysis

The Biomedical Computer Laboratory's involvement in clinical neurology, neurosurgery and in neurophysiological research reaches back to the Laboratory's beginnings. In 1965 and 1966 a LINC computer at BCL was applied in processing radioisotope brain-scan data transmitted over telephone lines from the hospital radiology unit, and in 1966 a LINC-controlled evoked-response display system was installed, providing neurosurgeons in the operating room with continuous EEG monitoring capability via closed-circuit television. That same year the NIH SAAM compartmental-analysis simulation and model-building program was implemented on the University's IBM System/360 Model 50 computer and this program has been used extensively since then in biological modeling and data processing. Regional cerebral blood-flow studies initiated in 1967 used magnetic-tape data acquisition, with later processing on the Model 50. In 1969 and 1970 a LINC computer was interfaced to a six-probe system designed by the radiology department for in-vivo cerebral blood-flow and oxygen-metabolism studies employing cyclotron-produced radioisotopes. A complete software package was developed to aid in data acquisition, analysis, storage, plotting, and display. The next two years saw further development of this approach with the construction of a twenty-six-probe brain blood-flow and metabolism unit capable of increased spatial resolution.

At this juncture, it was recognized at BCL that new initiatives in central nervous system and other radiotracer studies must stem, in part, from an improved understanding of the manner in which the underlying physiological phenomena reveal themselves through gamma rays and annihilation photons to the external data-gathering instruments. Thus, in collaboration with scientists at Washington University and at other institutions, the Laboratory undertook a substantial augmentation of its program in tracer kinetics by expanding its activities in physiological modeling and parameter estimation. These collaborative efforts led to successful quantitative methods of studying in-vivo such diverse processes as brain-glucose transport and metabolism, blood-brain-barrier permeation of water, alcohols, ammonia, and carbon dioxide, and the autoregulation of cerebral blood volume and blood flow.

The development at Washington University of instruments for tomographic imaging using positron-emitting radionuclides has created, for investigators here and elsewhere, a potential for further advances in tracer studies of the intact brain. Accurate in-vivo measurement of metabolic activity at specific anatomic sites made visible with the new technique should lead to further understanding of brain function and to an even greater utility of radiotracers for clinical and surgical applications. Further development at BCL of a computerized system for creating three-dimensional images of cerebral structures and lesions from transmission-tomograph data would appear to offer the neurosurgeon a convenient and beneficial alternative to his present dependence on examination of serial section scans. Similarly, the new developments sponsored jointly by BCL and the Division of Neurology and Neurological Surgery in automated monitoring of neuroelectric data give promise of future utility in the neurophysiology laboratory and in neurological medicine and surgery.

H-1. In-Vivo Measurements of Regional Brain Metabolism and Acid-Base Status

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In order to map, in-vivo and quantitatively, regional brain metabolism and acid-base status in humans we have developed tracer techniques employing ^{11}C-glucose and ^{11}C-bicarbonate. The annihilation radiation from the cyclotron-produced radioisotope ^{11}C is detected externally to image tracer distributions using positron-emission tomography[1] (PR 10, B-13; PR 11, B-7, B-8, B-9; PR 12, B-1, B-2, B-3, B-4, B-5).

Our technique for measuring regional glucose utilization (PR 12, B-4) is based on a modification of a previously described global method.[2] The modified approach employs a rapid infusion of radioglucose over a period of 6 to 10 minutes. The mathematical model on which our method is based shows how to use the specific-activity history of tracer in blood, together with a three-dimensional tomogram of brain obtained at the end of the infusion, to obtain quantitative regional metabolic rates for glucose. We have tested the method in adult rhesus monkeys,[3] obtaining whole-brain metabolic rates in the range of 4.5 to 6.8 mg min^{-1} hg^{-1}.

Our method has several advantages over others used in metabolic studies. First, and most importantly, it is an in-vivo technique. Next, we employ a tracer that is biochemically identical with the systemic traced substance. Thus, differences in blood-to-tissue transport or tissue-enzyme affinities need not be taken into account, in contrast with methods that employ analogues, such as deoxyglucose,[4] to trace systemic substances. Finally, the method is sufficiently general to allow its employment with a variety of suitable radiopharmaceuticals metabolized by brain, heart, or other organs.[5]

Our studies of brain-glucose metabolism have been complemented by quantitative emission-tomograph determinations of brain-tissue acid-base status. For these, we employed ^{11}C-labeled bicarbonate and carboxyhemoglobin carried in red cells. Equilibrium images of these two tracers enable us to measure the CO_2 brain-to-blood partition coefficient and, hence, to compute the regional brain CO_2 concentration. Our results are in accord with those previously reported[6] and yield tissue-pH values of 7.03 to 7.05.

The two techniques described are being used currently for studies in humans with a variety of pathological conditions.

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H-2. A Mathematical Model for Measurement of Glucose Transport in Isolated Brain Preparations Using ^{3}H-Glucose

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A single-injection, dual-indicator outflow-detection technique was used recently by colleagues at the University of Wisconsin to measure unidirectional transport of glucose from blood into isolated dog-brain tissue.(1) Their method makes use of ^{3}H-glucose, together with ^{22}Na as an intravascular reference marker, to calculate fractional extraction of the radioglucose tracer on a single passage through the brain vasculature following rapid injection into the internal carotid artery. Concentration histories of the two radioisotopes were followed in venous blood collected from the confluence of sinuses. The data were analyzed by the now widely accepted method of Yudilevich, et al.(2)

Subsequently, we developed and tested a new model at Washington University, based on external detection of radiation from ^{11}C-label glucose.(3) Since this model is the basis for our currently evolving method for in-vivo measurement of regional brain metabolism (H-1), we wish to cross-check the two independent approaches in order to help in making judgments concerning the fidelity of each. For this purpose we have obtained several sets of data from the Wisconsin group with the objective of analyzing them on the basis of our model equations, suitably recast in outflow-detection form. Resulting estimates of our model parameters, such as forward-to-reverse glucose flux and brain free-glucose turnover time, will be examined for consistency with our previous results.

As a first step in accomplishing the comparisons we have fit the ^{22}Na data with sums of gamma functions through use of our implementation of a previously described nonlinear parameter-estimation procedure.(4) The resulting parameterized function, when convolved with the impulse response of our model, will yield a new function that can be used in estimating the physiological parameters to be examined.

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H-3. Processing and Display of Neurophysiological Data

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NS 06947
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The PC-1200 data-display and manipulation software for the processing of IDAS-generated LINC magnetic tapes has been expanded as previously proposed (PR 12, H-19). The filter package has been expanded and modified in order to ease its use. In addition, sequential averages can now be rastered and software has been written for rastering, summing, scaling, etc., of data generated by recording the discharges of individual neurons as time events.

The system is now sufficient to display and manipulate all data generated by IDAS and is used routinely in our laboratories.

H-4. Studies in the Ventral Lateral Nucleus of the Cat

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Support: NS 04513
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Studies of the visual function of the ventral lateral geniculate nucleus in the cat employ ocular stimulation and microelectrode recording

of single unit action potentials in that structure. These events, converted via a voltage "window" discriminator to a sequence of pulses, are collected into post-stimulus histograms with a LINC computer and appropriate interface devices.

A program written in PC-1200 FORTRAN scales and displays these data on a scope in the form of histograms and graphs. Hardcopies of the displays are obtained from the Artronix model 1641 Hardcopy Unit for further analysis and laboratory records. Higher quality histograms also can be produced on the Versatec Matrix plotter. An index package allows the updating and displaying of experiment indices created on data tapes. A data-storage location package permits the storing and handling of up to three standard-length LINC tapes on the same storage bank of a disk.

H-5. Development of an Automated System for the Monitoring of Epileptic Patients with Indwelling Electrodes

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NS 06947
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We wish to record an EEG for up to 16 channels from indwelling electrodes and simultaneously record the patient's behavior on video tape. When a seizure occurs we must be able to extract and save both the video and EEG for several minutes before and several minutes after the onset. Finally, the EEG must be displayed with the simultaneous video image of the patient on a split television screen and the EEG written on paper in the conventional fashion.

Currently the EEG is monitored by a video camera focused on the first few inches of paper from a Grass 16-channel EEG machine. This signal is displayed along the bottom of a split television screen with the image of the patient at the top, enabling simultaneous study of the two records. The composite video signal is recorded on video tape also. When a seizure is noticed by a trained technician the location on the video tape and the page numbers spanning the seizure are noted and saved. Later the composite video may be reviewed and details of the electrical activity may be seen on the original EEG paper recording.

Currently we are constructing a system based on MECCA (A-14), capable of detecting a seizure and generating a video tape showing the patient and the EEG together on a split television screen accompanied by a conventional 16-channel EEG paper recording. To guide us in this task we have specified several desirable features the system must have. The duration of the recordings will be approximately 10 minutes and will be centered about the seizure onset. The system is to be automated to the extent that once it is activated, it will produce a series of six or seven recorded seizures without operator intervention, thus enabling continuous night-time monitoring to be performed. The system will have the capability of choosing its inputs from multiple-electrode arrays containing up to 80 contacts. Finally, the system must not interfere with the efficiency of other routine diagnostic procedures, such as collection of somatosensory evoked responses, direct stimulation of the brain, or continuous recording in our usual manner.

H-6. Three-Dimensional Display of Cerebral Ventricles

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Support: RR 00396

Accurate visualization of the cerebral ventricles and intracranial lesions is a necessary element of the planning for neurosurgical treatment. The rapid development of computerized axial tomography (CT scanning) has contributed a new tool to aid in this visualization. The greatly improved resolution in X-ray absorption over conventional X ray allows better visualization of normal and abnormal anatomical structures. Even with these significant improvements, considerable imagination is required of the neurosurgeon in order to make the transformation from what is seen in serial section CT scans to the spatial relationships needed to actually perform the surgery.

In an effort to assist in this transformation a three-dimensional representation of the right lateral cerebral ventricle has been implemented on an MMS-X graphics system.(1) With this implementation experiments have been performed to evaluate the effectiveness of the MMS-X display in depicting this three-dimensional structure.

The data corresponding to fifty cross sections were digitized and entered manually, using an atlas of CT scans and photographs of frozen sections as reference. The interval between sections roughly corresponds to the resolution available with current CT scanners. Initial reactions

by the medical staff have been enthusiastic, with the feeling that the display gives a good representation of spatial relationships with either stereo or motion-cue technique.

Current experiments are focused on evaluating similar displays with fewer sections since economics and X-ray exposure preclude the use of a large number of sections in the actual clinical setting. In an effort to recover some of the realism lost in using fewer sections the "chicken-wire" technique used successfully in applications of the MMS-X system to electron density mapping will be evaluated.

(1) C. D. Barry, R. A. Ellis, F. U. Rosenberger, B. Mitchell, D. Sawyer, and G. Johns, "MMS-X," in Washington University Computer Laboratories Annual Report, 1973-1974, pp. 216-237.

I. Supporting Activities

Activities at BCL which contribute to the goals of more than one of the major programs of the laboratory or to the needs of individual users who can benefit from the special expertise of the staff and the inventory of computer and test equipment are called supporting activities. Service to users does not follow the usual computation-center pattern. No fee schedule has been established, nor is there a centralized facility. Instead, senior laboratory staff members consider requests from investigators for assistance in biomedical computing. Some investigators may be directed to commercial vendors or existing fee-for-service facilities. Others may be advised of the unavailability of appropriate technology. The remaining investigators may have problems that match the special capabilities within BCL. Usually, such a project is assigned to a staff member with similar previous experience. If the project can be completed quickly, the investigator has his results and a short note describing the work will appear in the annual report and in the open literature if appropriate. Other projects occasionally prove impractical and the best alternative is recommended. A few of the user projects may develop into major initiatives within the laboratory. Most of the present successful projects began in this fashion and we value the opportunities that such projects provide.

Although the projects reported in this section span a variety of topics, they can be grouped conveniently as biomedical applications, system development aids, or digital hardware designs. The biomedical applications represent new initiatives in which basic exploration is being conducted which may or may not ultimately result in a major, long term program. The collaborative effort with the Department of Ophthalmology relating to the acquisition and processing of visual fields, and the investigation of the new techniques for radiation dose calculation with the Division of Radiation Oncology are examples. Even in cases where an extended effort does not materialize, the relationships which are cultivated frequently prove beneficial to future work.

System development aids mostly benefit the BCL staff but also are utilized by other groups where appropriate. An excellent example here is the microprocessor development support system which, although still evolving, is an almost routine tool used in data acquisition, signal processing, and control applications. The general purpose M6800 microprocessor P.C. card and the AUGAT wirelist program reported here are also widely used in supporting a variety of projects.

The digital hardware designs reported in this section are frequently one-time, special purpose designs. The Versatec switch and CDC Disk Exerciser fit this description. In contrast, other designs may have wide appeal and construction of multiple copies can easily be envisioned. The USD (Universal Storage Device) is such a design and is eagerly anticipated by users with a need for off-line data acquisition and local mass storage.

I-1. Visual Fields and Ocular Hypertension

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Interactive programs have been developed for digitization of visual fields extracted from the charts of patients followed in the Glaucoma Center of the Department of Ophthalmology. These data have been used to characterize statistical parameters for the normal population.[1] Work currently underway will utilize visual field data, along with the factors of ocular tension and optic cup morphology, to generate a predictive model for the probability of visual field loss in subjects with ocular hypertension.

Initial work has shown that both normal and abnormal visual field contours can be both encoded and reconstructed using Fourier series coefficients. Future plans include the development of algorithms for the extraction of specific pathologic features, using the Fourier transform representation of the plane closed curves of the recorded field contours.

[1] W. M. Hart, Jr. and B. Becker, "Visual Field Changes in Ocular Hypertension: A Computer-Based Analysis," Archives of Ophthalmology, vol. 95, pp. 1176-1179, 1977.

I-2. A Microprocessor-Based Data Acquisition System for the Goldmann Perimeter

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EY 00336

There is growing interest in the automated manipulation of visual field information for rapid cross-population statistical studies, quantitative temporal analyses of individual patients, and three-dimensional graphic

representations. Initial studies using the PC-1200 have employed the Rho-Theta position transducer to trace the contours of visual fields from existing patient records (PR 12, H-16). However, to reduce manual error and the need for this intermediate data transfer, it is desirable to acquire digitized field information at the time of patient interaction. Therefore, an engineering prototype has been developed for an on-line, microprocessor-based system that interfaces with the Goldmann perimeter and acquires and stores visual field information in computer readable form. This system explicitly does not attempt to replace the perimetrist, but provides the ability to obtain the digital information at a reasonable cost without complicating the established operational procedure.

The M6800-based system possesses two modes of data entry. Acquisition of patient related demographic data is performed through a keyboard with an alpha-numeric display verifying proper character entry. The necessary data to define a threshold point are obtained from stimulus setting and point location transducers. These involve noting the pattern of energized magnetic reed switches that are mounted in discrete stimulus setting positions and performing the sonic triangulation of a cursor attached to the pantographic linkage of the perimeter. The point information is transformed into Cartesian coordinates referenced to the center of the field and temporarily stored in a specific memory block determined by its stimulus setting.

An oscilloscope furnishes immediate feedback concerning the validity of each pair of stored coordinates, which allows the operator to delete erroneous points from temporary storage. An x-y plotter is employed to create a copy of the final set of points. After sequentially ordering each isopter by nearest-neighbor, both demographic and isopter information are saved on a floppy disk. Although the disk provides future reference and data transfer to a minicomputer, a serial link is supplied as an optional transfer path.

Present concerns include evaluation of accuracy, development of a calibration routine, and user evaluation to determine ease of operation and influence on operational procedure.

I-3. Radiation Treatment Planning

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The detailed and precise three-dimensional anatomic characterizations recently made possible by computerized tomography have motivated us to re-examine the problems posed by limitations of current radiation treatment planning approaches. Accordingly, we have devoted effort toward improving the accuracy of treatment plans by exploring possible methods of calculating three-dimensional absorbed-dose distributions in the presence of inhomogeneities of arbitrary sizes and shapes and with regular and irregular fields, capitalizing on the detailed anatomical information obtainable with computerized tomography. Our initial investigations have centered on a method, the basis for which is an idea suggested by J. R. Cunningham.[1] Unlike most current treatment-planning schemes, our proposed method appeals directly to established physical principles governing the interaction of electromagnetic radiations with matter at the atomic level. The method makes use of published experimental data describing the separate contributions to absorbed dose in water phantoms of primary and scattered components of the radiation from a given source. These data,[2] known as tissue-air ratio (TAR) and scatter-air ratio (SAR), can be used rigorously only for dose computations in homogeneous water-like soft-tissue regions. They are appropriately modified in the present method to account for the presence in the irradiated volume of structural inhomogeneities whose attenuation, scattering, and absorption properties differ from those of the water reference medium. These anomalous effects can be approximated to first order if, as presupposed, detailed tomographic information is available on patient composition in terms of electron density.[3] A brief description of our approach follows.

For photon energies commonly employed in radiotherapy, Compton scattering is the dominant mechanism for interaction of the primary source photons with the irradiated tissue. The TAR and SAR data describe the absorbed dose due to primary and scattered radiation of all orders at a

point in a water phantom relative to the measured primary dose at the same field point in air. Compton attenuation and scattering coefficients are proportional to electron density; thus, to compute a first-order correction to the SAR data, it suffices to scale the measured effects in water by the ratio of electron densities in the patient to the (known) electron density of water. Contributions to absorbed dose at a given field point in water arising from scatter at an arbitrary point in the irradiated volume are deduced by three-dimensional differencing of the SAR tables to obtain the differential effect of a small volume element, (hence the term "delta volume"). The relative differential scatter contribution of an arbitrary volume element in a patient to absorbed dose at the dosimetric point can then readily be obtained by electron-density scaling. After computing the relative attenuations in the patient (again, by electron-density scaling) along the ray paths from source to volume element and from there to the point of interest, the total scatter component of absorbed dose is obtained by summation over the entire irradiated volume. The attenuated primary component is evaluated in a similar way from the patient electron density along the primary-ray path. This contribution is then added to the scatter component to obtain total absorbed dose at the dosimetric point. Repetition of this procedure yields a three-dimensional matrix of absorbed-dose values throughout the volume of interest.

An objective of our initial work has been to investigate the validity of the mathematical model on which the delta-volume method is based. For this purpose, we compared theoretical values of absorbed dose computed via our method with some published experimental results of Young and Gaylord[4] obtained in studies using water phantoms of relatively simple geometry. We used the Washington University IBM System/360 Model 65 to carry out our calculations. In their experiments, Young and Gaylord simulated the effect of inhomogeneities by interposing thick absorbing blocks between their ^{60}Co gamma-ray source and their radiation detector. Their inhomogeneity materials were aluminum, carbon, foamed plastic, and air, corresponding to a nearly 2000-fold range of electron densities. Our computed absorbed doses were in excellent agreement with their published values, the relative deviations being less than one percent over a wide range of phantom configurations and inhomogeneity electron densities. We are, therefore, encouraged to believe that our approach can achieve similar precision in more realistic phantom and patient studies planned for the future.

(1) J. R. Cunningham, "Scatter-air Ratios," Physics in Medicine and Biology, vol. 17, p. 42, 1972.

(2) H. E. Johns and J. R. Cunningham, The Physics of Radiology, Third Edition, C. C. Thomas, Publisher, Springfield, Illinois, 1971.

(3) R. A. Rutherford, B. R. Pullan and I. Isherwood, "Measurement of Effective Atomic Number and Electron Density Using an EMI Scanner," Neuroradiology, vol. 11, pp. 15-21, 1976.

(4) M. E. J. Young and J. D. Gaylord, "Experimental Tests of Corrections for Tissue Inhomogeneities in Radiotherapy," British Journal of Radiology, vol. 43, pp. 349-355, 1970.

I-4. Microprocessor Development Support

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Support: RR 00396

Our microprocessor support capability, which consists of a FORTRAN-based cross-assembler, FOCRAS (PR 12, H-2), an intelligent console (InC) (PR 12, H-3), and a ROM programmer (PR 12, H-4), has matured and is being applied to several current project activities.

The cross-assembler, currently available as FOCRAS Version 4,[1] was rewritten in a subset of ANS standard FORTRAN to achieve the goal of portability between minicomputer hosts of various manufacturers. Assembler design improvements also yielded larger symbol tables and an approximate factor of 4 decrease in assembly time.[2] Large program sizes (e.g. 6000 bytes of code for CSL's Broadcast Information System) and the desire to establish a library of shared routines have resulted in the preliminary design of a linking loader.

The target-microprocessor adaptability of the InC was used to provide console support for our INTEL 8080 microprocessor activity. An 8080 dependent logic card and plug and an 8080 control microprogram were developed.

The facility with which the InC provides ability to capture and display internal register contents, to operate with different microprocessors, to provide a comfortable interface between the user and the processor, and to provide a communication link for loading the target from the files cross-assembled on the host minicomputer, has placed heavy demands on the availability of the instrument. Since additional InCs are needed to support our microprocessor activities, the decision was made to base a second generation design of the InC on an M6800 microprocessor. The redesign has been completed and fabrication is to be initiated shortly. Gains with respect to instrument maintainability and extendability are anticipated.

(1) D. Ungar, J. Blaine, M. Browder, and B. Spenner, "User's Guide for the FOCRAS Family of Cross-Assemblers," BCL Monograph No. 304, April 1977.

(2) D. Ungar, J. Blaine, M. Browder, and B. Spenner, "Microprocessor Development Support-Software Viewpoint," BCL Monograph No. 291, May 1977.

I-5. System Design Aid Planning

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T. C. Perry, M.S., Computer Systems Laboratory
J. A. Ritter, BCL
F. U. Rosenberger, D.Sc., Computer Systems Laboratory
B. F. Spenner, BCL
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Support: RR 00396

Application of digital technology to the solution of biological and biomedical computing needs often requires the development of specialized computer interfaces and complex special purpose computing hardware. The design of these digital systems involves careful attention to numerous local and global timing and electrical loading details, a sizeable amount of checking, design verification, production of technical documents, and generation of instructions needed for system fabrication, testing, and maintenance.

Preliminary studies of commercially available digital design aids (DDA) systems indicated that, while many of the desired features existed in disparate systems, none is available that provides the vertical integration we feel is necessary for substantial improvement in our complete design cycle. A study group under the direction of Dr. Wann has reviewed DDA systems and components in both the commercial and academic communities.

Commercial systems represented by Applicon Corporation, ADAGE, Computer Vision, and REDAC encompass logic drawing generation aids, wirelist generation, and interactive printed-circuit board layout with varying degrees of success. The only commercial offering found which addresses the logic verification problem is a service available via Control Data Corporation's Cybernet. Test Generation and Simulation (TEGAS) satisfies many of the needs for systems composed of small scale integrated circuits, but is limited

since a library of the more complex integrated circuits has not been included.

Activity in the academic community has created a number of "local" design aids with insufficient documentation to encourage portability. An exception to this is Stanford University's drawing package, (SUDS), which is an interactive graphics system. The host computer, a PDP-10, limits applicability in our environment.

The study effort culminated in a recommendation of the scope of required activity to specify and develop a vertically integrated minicomputer-based system for aiding digital system design.[1]

[1] "1977 WUCL Renewal Application, Research Plans, Initiatives in Computer System Designs," System Design Aids, pp. 129-134.

I-6. Studies of a Unified Approach to Data Acquisition, Processing and Display

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Support: RR 00396

The range of biomedical computing needs, to be addressed in our local research community, is describable at the conceptual level by a small set of functional categories: experiment control, data logging, data analysis, and sense/alert. Several or all of the functional categories may be involved in a particular application in laboratory or clinical research.

A system implementation satisfying the functional requirements for a particular application can be optimized in a "local" sense. The resulting implementation is likely to be tuned in such a way that portability to other application areas suffers. A study was initiated to examine feasibility of a unified approach to the development of digital systems which enhances the portability of system components, both hardware and software, over a wide range of application areas.

The initial phase of the study reviewed the requirements of current research activities in laboratory biochemistry (F-1), physiologic research (C-3), (A-18), and speech and hearing (G-3). The constraints considered include environmental (space, noise, power), processing capability (speed, power), storage facility (volume, access), display, cost (available equipment funds, development costs, and maintenance), time (start-up, life), and flexibility of an initial solution.

A single system implementation with sufficient capability to satisfy the worst-case set of performance constraints would likely fail the cost and flexibility constraints. An alternate approach suggests a utopian set of hardware and software modules. The attendant problems with such an approach include the usual concerns:

1) module library must be expanded to include "too many" special types,
2) cost overrun,
3) long development time/large initial investment,
4) technology may make obsolete the approach.

The separation of each application problem into tasks which can be addressed with individual processors seems to offer the degree of modularity which could soften the portability problem. The degree of integration occurring with microprocessors (processor, clock, I/O, storage in a single chip) should allow I/O controllers and signal preprocessors to be fabricated at "near-zero" hardware cost. The clustering of the modules into capable systems requires a standard interconnect (or family of interconnection standards) which is well specified functionally, mechanically, and electrically.

The compartmentalization provided by the modular approach with standard interconnect should allow the evolution of a "module" inventory to take advantage of new processor/storage/etc. technology. Preliminary study of standard interconnect and communication protocol has included both recognized and defacto standards: IEEE-488 (Digital Interface for Programmable Instrumentation), CAMAC, Digital Equipment Corporation's UNIBUS, EIA serial, ANS I/O Channel Interface (proposed), and programmed parallel digital I/O interfaces for TI, DEC, and Interdata, and Data General minicomputers.

I-7. Physiologic Signal Processing

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Support: RR 00396

Analyzing physiologic signals in terms of their frequency spectra is an extension of previous work[1,2,3,4,5] aided by the application of an efficient moving window discrete Fourier Transform.[6] The work completed during the past year was mostly developmental and focused on the analysis of ECG records. The ECG was chosen as a starting point because of existing resource expertise. We do intend, however, to look beyond ECG processing toward the application of these analysis strategies to other physiologic signals such as EEG, intravascular or intracardiac pressures, instantaneous blood or gas flow, and even temperature.

At present, the analysis window is adjusted to encompass the signal resulting from only one cardiac cycle (P wave to T wave). The results from the transform are being analyzed in an attempt to correlate different signal morphologies with the resulting shapes of the amplitude spectra. The fiducial point for the amplitude analysis is specified presently as a function of the amplitude coefficients. In future work possibly a more appropriate procedure will use the phase coefficients as they express the time dependent nature of the signal.[7]

In the past year, FORTRAN programs that operate on the PC-1200 were developed to carry out preliminary studies using the Fourier analysis technique. A FORTRAN-callable subroutine, written in assembly language to optimize performance, calculates the Fourier coefficients of the signal in the analysis window, using the algorithm described by Dillard.[6] Another subroutine, also FORTRAN-callable, plots the transform results along with the signal being analyzed on a Versatec printer/plotter. Figure 1 shows the types of output generated by the use of the two aforementioned routines.

The recent addition of 9-track tape to the PC-1200 (I-15) will allow us to begin analyzing Argus-processed and labeled tapes (A-1). A number of these tapes will be analyzed and statistics gathered on the transform amplitude spectra. These statistics can then be compared with the Argus-generated labels, thereby generating statistics relating signal morphologies implied by the labels to the calculated amplitude spectrum statistics. As a result of these ECG studies we hope to develop a robust method for marking fiducial points and an improved technique for classifying signals by their features in the frequency domain.

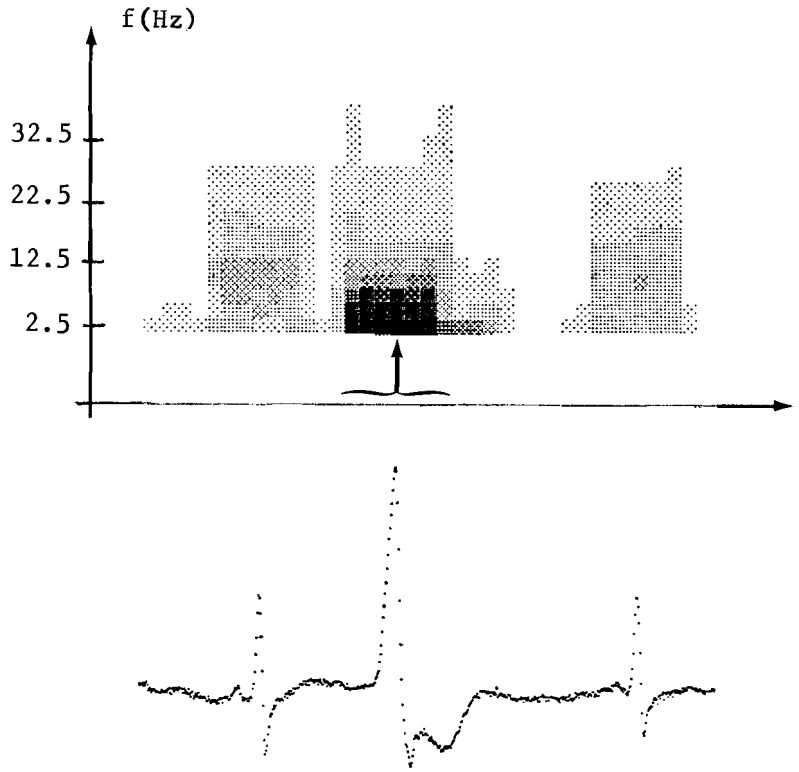

Figure 1. The amplitude spectrum of the ECG signal contained in a moving analysis window is plotted as a function of time. The grey scale is used to represent the amplitude of the frequency components. The darker areas result from components with larger amplitudes.

(1) D. P. Golder, R. A. Wolthuis, and G. W. Hoffler, "A Spectral Analysis of the Normal Resting Electrocardiogram," IEEE Transactions on Biomedical Engineering, vol. 20, p. 366, September 1973.

(2) R. C. Barr and M. S. Spach, "Sampling Rates Required for Digital Recording of Intracellular and Extracellular Cardiac Potentials," Circulation, vol. 55, p. 40, January 1977.

(3) R. Kitney, C. Turner and A. McDonald, "Assessment of QRS Shape and Measurement of Interbeat Interval as a Basis for ECG Rhythm Analysis," Proceedings of The Conference of Computers in Cardiology, IEEE Catalog No. 75 CH 1018-1C, Rotterdam, The Netherlands, pp. 37-40, October 2-4, 1975.

(4) O. W. Mortara, "A New Pattern Recognition Approach to Exercise Analysis," to be published.

(5) C. S. Weaver, J. Von Der Groeben, P. E. Mantey, J. G. Toole, C. A. Cole, J. W. Fitzgerald, and R. W. Lawrence, "Digital Filtering with Electrocardiogram Processing," IEEE Transactions on Audio and Electroacoustics, vol. 16, p. 350, September 1968.

(6) G. M. Dillard, "Recursive Computation of the Discrete Fourier Transform, with Applications to a Pulse-Doppler Radar System," Computation and Electrical Engineering, vol. 1, p. 243, January 1973.

(7) P. G. Amazeen, R. L. Moruzzi, and C. L. Feldman, "Phase Detection of R Waves in Noisy Electrocardiograms," IEEE Transactions on Biomedical Engineering, vol. 19, p. 63, January 1972.

I-8. Development of a General Purpose M6800 Printed Circuit Board and Interfaces

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Support: RR 00396

A general purpose printed circuit board employing the Motorola M6800 microprocessor has been developed to fill an increasing number of microprocessor applications. The processor card includes 256 bytes of read/write scratchpad memory and 1024 bytes of programmable-read-only memory for program storage. To insure adequate system expandability, both address and data busses are buffered. The startup address is specified by two 8-position DIP switches.

The decision to design a printed circuit card in-house was influenced by a variety of factors. Of primary concern was physical compatibility with the Augat wirewrap cards employed throughout the laboratory. There are several commercially available M6800 systems, but few of these have adequate bus buffering to permit system expansion. Most are physically large in order to accommodate memory expansion on the same board as the processor, and include one or more dedicated peripheral interfaces which would not be required in every system. Frequently memory and interface bus addresses are incompletely decoded, hampering system expansion. These factors strongly indicated the desirability of an in-house design.

The design was begun in September, 1976, and the prototype was

completed in December, 1976. After revision, several copies were produced by the Computer Systems Laboratory's printed circuit facility. These have been employed in diverse applications (H-5, I-2, I-7, I-12). Experience with these applications prompted further refinements and plated-through hole boards with socket inserts are now being produced for future needs.

In addition to the processor card, several support elements have been developed on Augat wirewrap cards. These include 4k-byte RAM and PROM cards for memory expansion, and general purpose interface cards for serial communication and analog-to-digital conversion. Two digital-to-analog conversion cards have been developed, one general purpose card and another tailored specifically for driving an X-Y storage oscilloscope. Each of these memory and interface cards is configurable by jumpers to occupy user-selected bus addresses, allowing the users to implement whatever combinations of memory and peripherals they desire. For prototype systems, another wirewrap card contains the necessary components to support MIKBUG, a Motorola-supplied debugging monitor.

I-9. Utility Software Development for the PC-1200

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OS/PC LIBRARY has been extensively modified and enhanced. Programmers for a variety of projects at BCL, Radiology, Barnes Hospital, and Jewish Hospital are making use of programs from the library and are suggesting new ones as required. Standard programming techniques making use of OS/PC LIBRARY programs are being adopted.

The library is organized as follows:

I. OS/PC COMMANDS (22)
II. SUBROUTINES (75)
- A. Disk
- B. Overlay
- C. Miscellaneous
- D. Character Display
- E. Index Manipulation
- F. Character String Processing
- G. Scope Display
- H. Plotting
- I. Mathematical

J. Data Conversion
K. Data Storage
L. Keyboard Handlers

III. FUNCTIONS (17)
IV. CORRECTIONS (4)
V. DOCUMENTATION (7)

In addition, utility programs for testing the Pertec disk and converting between PDP-12 and PC-1200 source code were developed. Programs for testing the Fast Fourier Transform and the uniform random number generator were written.

Investigations into improving the speed performance of the FORTRAN compiler for the PC-1200 were made and results showed that the execution times of FORTRAN programs which use floating point computation could be improved by as much as a factor of eleven by rewriting the compiler.

I-10. A Wirelist Program for Augat Hardware

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Support: RR 00396

A set of programs was developed to facilitate generation of legible, accurately transcribed wiring lists for projects implemented on Augat wire-wrap cards (PR 12, H-9). A step-by-step user's manual was completed in January, 1977, and its distribution expanded the use of the system significantly. There are currently 15 users who have entered almost 50 wiring lists which are maintained in on-line disk storage for ease of accessibility. Several features have been added to the original system, allowing the user to update a design more easily. New output formats have been implemented to improve the clarity of documentation produced by the wirelist programs.

Due to the expanding user community and consequent increase in size of the database, a significant restructuring of the larger elements of the database is planned. It is anticipated that this restructuring of variables in the database will decrease the amount of disk storage required, as well as improve the response time of the programs. This will allow implementation of further improvements to the updating facilities of the programs. Full program and database documentation will accompany the revision.

I-11. A Flexible Interface for Video Display

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Support: RR 00396

In order to better address the requirements of both current and projected applications of the clinical physiologic research cart (CPRC), a direct interface of the video display system to the CPRC internal computer became desirable. The early implementation of the CPRC depended upon reserve capability of the surgical intensive care unit (SICU) video display system, accessed via a serial communication link to the SICU computer, for the generation of alphanumeric and graphic displays returned as composite video to the CPRC over coaxial cable.

Instead of designing a special-purpose parallel interface to connect the TI-980 computer of the CPRC to a local video display system, it was felt that a more general approach was justified in order to allow ease of transition to a different computer in the future. Since most computers have an RS-232 serial interface as a standard product, it was felt that this type of connection to the video display system would provide nearly universal applicability. With this in mind, a functional specification has been developed, using a full-duplex, asynchronous communication protocol which, when operating at 9,600 baud, will support three graphic channels with delayed graphic return, all operating at 120 samples/second/channel, and one alphanumeric channel operating at 60 characters/second. Burst output of alphanumeric information can be accomplished at 400 characters/second if graphic output is suspended briefly.

Detailed implementation of the interface is in progress, using an M6800 microprocessor system as a control element. Characters received from the RS-232 link will be interpreted as commands and data by the M6800 and appropriate control signals will be generated by the firmware and sent to the video display system via parallel interface adapters (PIAs) attached to the M6800 bus.

I-12. The Universal Storage Device

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M. L. Smith, BCL

Support: RR 00396

The Universal Storage Device (USD) is designed to satisfy those data acquisition, storage, and retrieval needs that frequently occur in our laboratory where data are recorded at a remote site and then later retrieved and transferred to a computer system for processing. The USD is structured to satisfy the data acquisition needs of the local community as they were defined by a survey of potential users. The overall design objectives for the USD led to the implementation of a device that is portable, dependable, easy-to-use, and not overly expensive.

A user is provided with front panel access to one digital and four analog input channels (12-bit conversion) that can be independently enabled and disabled. Periodic sampling of the input channels can be done automatically by the USD with the sampling periods selected by the setting of a console switch. The sampling rate can be varied over the range from 0.5 samples/second to 2000 samples/second. The USD has the capacity to store over 800K bytes of data, which provides a recording time of 4.44 minutes at 2000 samples/second with one channel selected, and 3 days at 0.5 samples/second with 4 channels selected. The USD also can perform aperiodic sampling where the channels are sampled on command of an external device. A user controls the recording process with a single button that pauses and resumes recording, while two console indicators, "Time Remaining," and "Event," keep the user informed as to the state of the recorder.

The data stored in the USD are retrieved by transmitting it serially (RS-232) under the control of the external device that is accessing the stored data. Since the retrieval function allows an external device to store data as well as retrieve it, the USD can be used in retrieval mode as a mass storage peripheral that is easily connected to any system with an RS-232 compatible interface. The bandwidth of this external connection will soon be enhanced with the addition of a parallel bus that operationally conforms to the IEEE-488 standard.

I-13. A Selector Switch for the Versatec Printer/Plotter

Personnel: S. R. Phillips, BCL
R. E. Hitchens, BCL
B. F. Spenner, BCL

Support: RR 00396

A switching unit has been developed to allow a Versatec Printer/Plotter to be multiplexed between four computer systems. The computer to be connected to the Versatec is selected by depressing one of four momentary pushbuttons on the front panel. The necessary control and data lines are then connected electronically. The switching unit employs its own internal power supply so that no external power is required either from the Versatec or the computer.

I-14. A Disk Exerciser for CDC 9700 Drives

Personnel: S. R. Phillips, BCL
R. E. Hitchens, BCL

Support: RR 00396

A disk exerciser has been designed to allow control and alignment of any Control Data 9760 or 9762 disk drive. The exerciser is powered independently from the drive and is connected directly to the drive's I/O connector. Several variations are possible in both the "seek" and "head alignment" modes of operation. The exerciser is configured by setting BCD and toggle switches and eight test points are available for the connection of an oscilloscope or other test equipment. The exerciser is currently under construction.

I-15. Nine Track Tape for the PC-1200

Personnel: B. F. Spenner, BCL

Support: RR 00396

The telecommunications link that has connected our laboratory's minicomputers with the university's IBM System 360/Model 65 has been abandoned. This link was initially constructed to satisfy both the mass storage and complex computational needs of our laboratory projects. However, the recent decline

in the cost of mass storage has permitted its direct connection to the laboratory computers. The reduction of 360 link utilization that resulted from introducing local mass storage led to the decision to abandon the link, as its utilization did not justify the level of support necessary for its maintenance and operation.

Since the telecommunication link was no longer available and the need for access to the computational power of the 360 remained, a replacement link with the 360 had to be implemented. The connection of a tape system to the PC-1200 has provided the needed replacement link in the form of industry compatible 9-track tape.

A Pertec 9-track tape drive and buffered formatter were connected to the PC-1200 by using a slightly modified, commercially produced interface. FORTRAN-callable software utility routines are available to control tape motion and the transfer of data to and from the tape. A complete description of the system is provided in BCL Monograph No. 319.

VI. INDUSTRIAL COLLABORATION

One of the goals of the Biomedical Computer Laboratory is to foster the commercial development of useful medical computer systems. Industrial collaboration provides an additional outlet for laboratory developments and benefits the staff by keeping it abreast of the practical considerations of reliability, maintainability, and cost. Progress being made in this important phase of the laboratory's activities is summarized here.

A. Arrhythmia Monitoring. Following evaluation of the Mennen-Greatbatch ARGUS/SENTINEL computerized arrhythmia detection system, it was installed in the Barnes Hospital Coronary Care Unit. Subsequent to the successful completion of a battery of acceptance tests administered by BCL, it was released to CCU personnel for clinical use. The system has been in routine clinical use for over a year. This collaboration continues through sharing algorithm improvements of mutual interest.

In collaboration with Hewlett-Packard, BCL has recently completed a comparative evaluation between the HP 78220 computerized arrhythmia detector and Argus/H (A-12). Hewlett-Packard has supplied an ECG database (15 minutes on each of 14 patients) in analog form. The 78220 processed these data previously and computer annotations have been supplied. This evaluation clarifies performance-related questions for the two systems which have been designed according to very similar philosophies. (BCL personnel: H. D. Ambos, R. M. Arthur, G. C. Oliver, L. J. Thomas, Jr., K. L. Ripley, J. A. Ritter)

B. Reconstructive X-Ray Tomography. The previously reported work with Picker Corporation (PR 12, VI-B) was completed last year and has subsequently led to two patents:

Brunnett, C. J., Cox, Jr., J. R., Snyder, D. L., and Mattson, R. A., "Tomography System Having Nonconcurrent, Compound Axial Scanning," U.S. Patent 3,976,885, August, 1976.

Cox, Jr., J. R., and Snyder, D. L., "Transverse Tomography System Having Multibeam Orbital Scanning with All Beams Offset from the Center of Orbit," U.S. Patent 3,983,399, September, 1976.

C. Collaborative Drug Study. A research project has been in progress during the past year with Sandoz-Wander, Inc., for a pilot study to evaluate the safety and efficacy of a new beta-adrenergic antagonist, LB-46, on ventricular irritability. Following FDA approval of the experimental design the study was initiated in May, 1976, and will continue into next year. This Phase II study consists of a double-blind crossover against placebo, of four weeks duration for each of twenty ambulatory patients with twenty or more premature ventricular contractions per hour. In addition to the appropriate clinical observations and laboratory tests, seven 24-hour Holter tapes are being collected and analyzed via Argus/H for each patient. Beyond a substantial participation in the study design the primary role of the laboratory is analysis of the Holter tapes. Provision has been made for

optional analyses to include time-of-day-independent PVC rates as well as frequencies of couplets, runs, and early PVCs. Initial analyses of variance then would consider dependent variables as being either the number of couplets, runs, or early PVCs per 24-hour period, and the sources of variation as treatment, order of treatment, and patients.

The opportunity to examine the power of Argus/H for such studies is welcome. It is particularly appropriate that this pilot design-feasibility study is small enough not to compromise our on-going Argus/H-based research efforts (section V., A.) and yet allows us to examine system performance in the context of a carefully drawn drug study. The "machine-edit" algorithms reported last year (PR 12, A-15) have proven to be invaluable for this work. It is this type of study upon which systems such as Argus/H are likely to have a major impact. (BCL personnel: K. W. Clark, T. F. Martin, J. P. Miller, G. C. Oliver, L. J. Thomas, Jr., P. W. Webb)

VII. TRAINING ACTIVITIES

During the year the Biomedical Computer Laboratory engaged in the following training activities.

Programming for Medical Information Systems, Fall, 1975

A high-level programming language (Massachusetts General Hospital Utility Multi-Programming System - MUMPS), designed for medical information systems, was presented by Dr. Patricia Moore, with programming examples from hospital and ambulatory care settings. Attending the course were:

Khosrow Ahdoot, B.S.	Technology Health Care Student
John Aje, B.S.	Technology Health Care Student
Ken Altshuler, B.S., B.A.	Technology Health Care Student
Yousri Barsoum, B.S.	Technology Health Care Student
Linda Brandenburger, R.N.	Jewish Hospital
Richard Camuto, B.S.	Technology Health Care Student
Richard Eisner, B.S.	Technology Health Care Student
David Emerson, B.S.	Technology Health Care Student
Susana M. Fortun, B.S.	Technology Health Care Student
Eric Hagelstein, B.S.	Technology Health Care Student
Chandler Henn, B.S.	Technology Health Care Student
William H. Homer, B.S.	Technology Health Care Student
Margaret Hug	Biomedical Computer Laboratory
Gary J. Koenig, B.S.	Technology Health Care Student
Judah A. Levine, B.S.	Technology Health Care Student
Thomas J. Marshall, B.S.	Technology Health Care Student
Remo Moroni, III	Biomedical Computer Laboratory
Howard Neuwirth-Hirsch, B.S.	Technology Health Care Student
William Pickard, Ph.D.	Electrical Engineering
Eric Poe, B.S.	Electrical Engineering
Dennis Repinski, B.S.	Electrical Engineering
Chris Zobkiw, B.S.	Electrical Engineering

Introduction to Programming the Laboratory Computer, Spring, 1977

Students were introduced to the PC-1200 computer and its components, peripherals, software, and applications. The OS/PC Operating System, the FORTRAN/PC compiler, and OS/PC Assembly Language were presented. Problem sessions using the PC-1200 were held to familiarize students with loading the operating system, entering and editing programs, and running and debugging both FORTRAN and assembler programs. The course was taught by Mr. Stanley A. Garfield. Attending the course were:

Jim Buchana, B.A.	Neural Science Physiology
Hollace Cox, Ph.D.	Radiology
Ken Grant, B.A.	Central Institute for the Deaf
Allen D. Greenwalt, B.A.	Renal Division
William Johnson	Jewish Hospital
Stuart Jones, M.D.	Nuclear Medicine
Donn Kleinschmidt, B.S.	Neuroscience Anatomy
Judy Lauter, B.A.	Central Institute for the Deaf
William Miksirek	Central Institute for the Deaf
Richard M. Sachs, Ph.D.	Central Institute for the Deaf
Dana Sawyer, A.B.	Radiology
Brian Scott, Ph.D.	Central Institute for the Deaf
Don Sinex, B.S.	Central Institute for the Deaf
Harry E. Vink	Jewish Hospital
Paul M. Weeks, M.D.	Surgery
Lynn Wesselman	Barnes Hospital Admitting

Survey of Biomedical Computer Techniques, Fall, 1977

This series of presentations was directed toward biological scientists to provide an appreciation of the capabilities and limitations of digital computers as applied to biomedical problems. Topics included: elements of sampling theory relevant to computer processing of biological signals, computer fundamentals, implementation of a computer using macro-modules, software techniques including machine, assembler, and higher-level languages, and input/output devices. Microprocessor support, signal processing, and presentation of application techniques, as exemplified by existing systems (e.g. clinical and laboratory research systems), were included also.

Presentations were given by BCL staff members, R. M. Arthur, G. J. Blaine, K. W. Clark, V. W. Gerth, Jr., R. H. Greenfield, K. B. Larson, P. Moore, N. Mullani, D. L. Snyder, B. F. Spenner, and L. J. Thomas, Jr., G. C. Johns of CSL, and J. W. Lewis of Barnes Hospital. Attending the course were:

H. Dieter Ambos	Biomedical Computer Laboratory
Theron R. Baird	Biomedical Computer Laboratory
Mary Campbell, R.N.	Cardiology
Gerry Clarke	Cardiology
Peter Corr, Ph.D.	Cardiology
Ronald Hagen, M.S.	Biomedical Computer Laboratory
William M. Hart, M.D., Ph.D.	Ophthalmology
Phyllis S. Hershey, M.A.	Dean's Office
Stuart A. Jones, M.D.	Nuclear Medicine
Remo Moroni, III	Biomedical Computer Laboratory
Satish C. Prasad, Ph.D.	Radiology
Wayne Roloff, B.S.	Biomedical Computer Laboratory
William Yakstis	Biochemistry

VIII. SEMINARS

During the year the following seminars were sponsored by the Biomedical Computer Laboratory.

"A Computerized System for Studying Natural Speech Sounds" July 2, 1976	Dr. Victor W. Zue Department of Electrical Engineering Massachusetts Institute of Technology Cambridge, Massachusetts
"Characteristics of Clinical Data Bases and Their Usage" August 11, 1976	Mr. Robert H. Greenfield Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"Introduction to M6800 Microcomputer and Support Facilities" (jointly sponsored by the Departments of Computer Science and Electrical Engineering) November 1-3, 1976	Dr. G. James Blaine Mr. Ross K. Hartz Dr. Bruce F. Spenner Mr. David M. Ungar Biomedical Computer Laboratory and Mr. Robert Ellis Computer Systems Laboratory Washington University St. Louis, Missouri
"Measurement of Cardiovascular Shunts by Computer Analysis of Thermodilution Curves" February 24, 1977	Dr. Christopher A. Cutler Department of Biophysics Primary Children's Medical Center Salt Lake City, Utah
"Operational Characteristics of Magnetic Bubbles" February 25, 1977	Dr. Bruce F. Spenner Biomedical Computer Laboratory Washington University Medical School St. Louis, Missouri
"Informal Discussion of Anti-arrhythmic Drug Trials in Europe" March 1, 1977	Dr. Paul G. Hugenholtz Thoraxcentrum Erasmus University Rotterdam, The Netherlands

"A Statistical Approach to Rhythm Diagnosis of Electrocardiograms"

March 24, 1977

Dr. Donald E. Gustafson
Scientific Systems, Inc.
Cambridge, Massachusetts

"Technology in Rural Health Care"

May 6, 1977

Dr. Maxine L. Rockoff
National Center for Health Services Research
Rockville, Maryland

"Segmented Approximation of Second-Order Random Processes with Application to Vectorcardiogram Representations

May 27, 1977

Dr. Sanjoy Mitter
Electronic Systems Laboratory
Massachusetts Institute of Technology
Cambridge, Massachusetts

IX. PUBLICATIONS AND ORAL PRESENTATIONS

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Clark, K. W., Ambos, H. D., Mead, C. N., Hitchens, R. E., Oliver, G. C., and Thomas, Jr., L. J., "Argus/H: A Computer System for Rapid Analysis of Long-Term ECG Recordings," accepted for presentation at the First Annual Symposium on Computer Application in Medical Care, Washington, D. C., October 3-5, 1977.

Clark, K. W., Moore, P., Miller, J. P., and Thomas, Jr., L. J., "A Total Systems Approach to Quantitative Analysis of Holter-Recorded ECGs," accepted for presentation at the Second International Symposium on Ambulatory Monitoring, Harrow, England, September 12-14, 1977.

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X. MONOGRAPHS

The Biomedical Computer Laboratory's Monograph Series was established to systematize the many informal reports, reprints, program descriptions and other documents written at BCL or supported by some of the Laboratory's facilities or staff. Following is a list of the monographs published by BCL during the past year. Copies of the complete index to the Monograph Series are available on request.

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299	Zimmerman, J. Kuthe, G.S. Stimac, R.K.	MUMPS Application Design Manual for Dictionary	9/76
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301	Zimmerman, J. Malamud, R.S. Stimac, R.K.	MUMPS Application Design Manual for DOC, a Documentation Package	9/76
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